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Depression in Patients with Diabetes: Risk Factors, Medication-taking Behaviors, and Association with Glycemic Control

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by

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Depression in Patients with Diabetes: Risk Factors, Medication-taking Behaviors, and Association with Glycemic Control

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This study evaluated the epidemiological relationship between diabetes and incident depression, as well as antidepressant medication utilization among indigent care patients diagnosed with diabetes. Medical data for 2,886 subjects receiving care in a public indigent care provider network were utilized for this study. Diagnoses of diabetes, depression, and other comorbid medical conditions were identified from the electronic medical record. Prescription claims data from the clinic pharmacy network were used to evaluate medication-taking behaviors. Clinical laboratory data were extracted, as available, from the electronic clinic records.

After controlling for the influence of age, gender, race/ethnicity, marital status classification, and Charlson score, a diagnosis of diabetes was associated with a 42 percent reduction in odds of new-onset depression ($p = 0.021$). In the *a priori* analysis of factors associated with new-onset depression among diabetic patients, none of the risk factors evaluated were associated with incident depression at a statistically significant

level. Post-hoc exploratory analyses revealed that female gender and White non-Hispanic race/ethnicity were associated with increased odds of a prevalent diagnosis of depression among diabetic patients. Patients with diabetes were more likely to be prescribed selective serotonin reuptake inhibitors (SSRIs) as their initial antidepressant medication compared to non-SSRIs. Diagnosis of diabetes was not associated with antidepressant switch, discontinuation, or 6-month antidepressant adherence; however, diagnosis of diabetes was associated with a higher level of 12-month antidepressant adherence ($p = 0.024$). Diagnosis of diabetes was also associated with a higher level of 3-month antidepressant persistence ($p = 0.004$), but not 12-month persistence. There were no statistically significant relationships observed between initial class of antidepressant medication prescribed and any of the medication-taking behaviors evaluated. For subjects with available data ($n = 106$), glycemic control was evaluated in terms of hemoglobin A1c. Increased antidepressant medication adherence was associated with higher hemoglobin A1c values during follow-up.

Results suggest that prevalent diabetes is associated with a reduced risk of diagnosis of new-onset depression in indigent care patients. Further research is necessary to evaluate the effect that chronic comorbid medical conditions such as diabetes may have on antidepressant medication-taking behaviors, and the relationship between antidepressant exposure and glycemic control.

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Chapter 1: Introduction and Literature Review

PROBLEM STATEMENT

As clinicians increasingly embrace a holistic approach to understanding the health status of their patients, greater attention has been given to the interaction between chronic medical conditions and comorbid psychiatric disorders. Of particular interest to many has been the effect of comorbid mood disorders on chronic diseases such as hypertension, cardiovascular disease, and diabetes mellitus. A number of studies have indicated that chronic medical conditions may be exacerbated when comorbid depression is present. Patients with concurrent psychiatric and chronic medical conditions utilize more healthcare resources, experience greater loss of productivity, and display increased functional impairment compared to their non-depressed counterparts. While recent attention has focused on the complex interactions between mental illness and a variety of chronic medical conditions, relatively little research has been conducted focusing on the implications of medical and psychiatric comorbidity on psychotropic utilization patterns, psychotropic medication adherence and persistence, and other factors related to medication treatment in these patients. The purpose of this research is to evaluate the relationship between diabetes and new-onset depression, and to explore the potential implications that comorbid diabetes and depression may have on medication-taking behaviors and patient clinical status.

INTRODUCTION

The notion that a relationship exists between psychiatric disorders, emotional well-being, and physical health is not a new concept. "A cheerful heart is good medicine, but a crushed spirit dries up the bones" writes the author of the Biblical text Proverbs, noting the link between emotional and physical well-being.[1] In the 3rd century CE, the Roman philosopher and physician Galen speculated that physical and psychological maladies were related to a common etiology. He suggested that melancholic disposition and breast cancer in women were related to a common underlying imbalance in black bile.[2] The 12th century Rabbi Moshe ben Maimon comments in his work, *Regimen of Health,* that the "passions of the psyche produce changes in the body that are great, evident, and manifest to all".[3] Further, Maimonides suggests that a primary role of the physician is to address these psychological barriers to wellness. In more recent times, Thomas Willis, the originator of the term *diabetes mellitus* in the late 17th century, noted the association between glycosuria and mood. Willis suggested that diabetes resulted from "sadness or long sorrow and other depression and disorders".[4]

Despite historical recognition of the relationships between the mind, emotional well-being, and the body, modern medicine is only beginning to fully appreciate the biological basis of these associations and their clinical consequences. In the 300 years since Willis' observation, scientific research focused on the relationship between diabetes and depression has been scarce. Indeed, most of the scientific literature on the subject has only emerged in the last 20 years. This chapter will provide a brief overview of major depressive disorder and diabetes mellitus, including a review of the epidemiology, diagnosis, and treatment of each disorder. This chapter will also summarize the current understanding of the relationship between depression and diabetes, and review the

research evaluating clinical outcomes among individuals with diabetes and comorbid depression.

MAJOR DEPRESSIVE DISORDER

Epidemiology

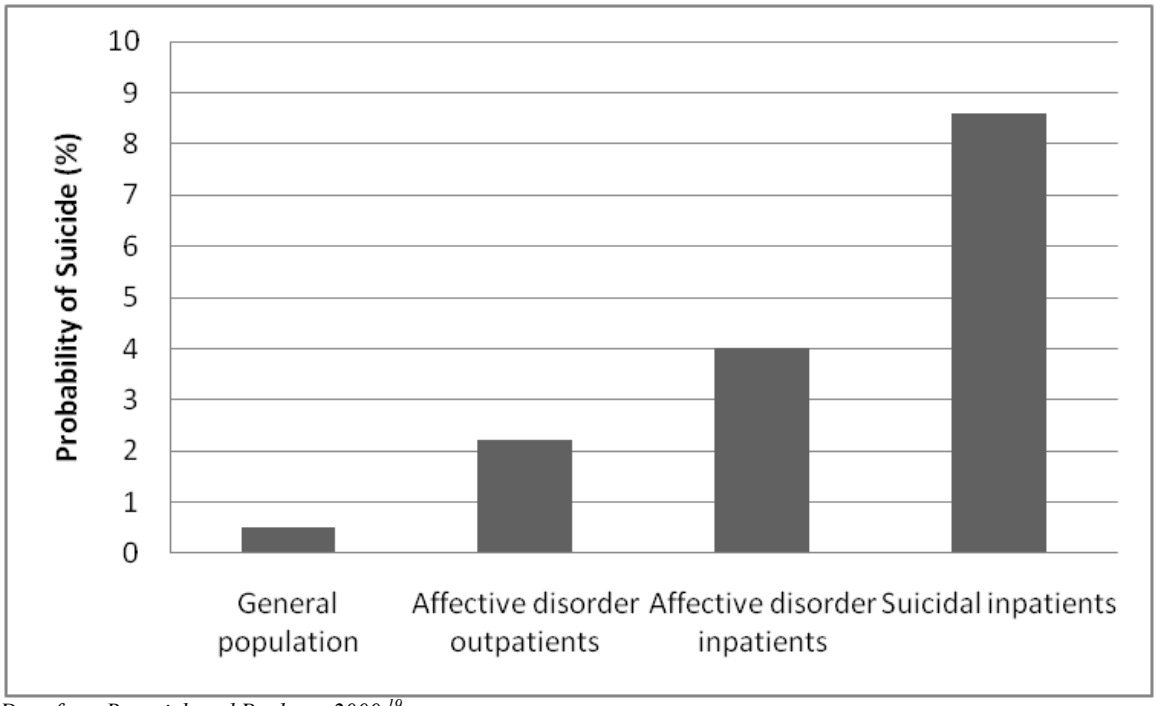
Major Depressive Disorder (MDD, referred to simply as depression hereafter) is a severe and disabling psychiatric mood disorder affecting approximately 6 percent of Americans each year.[5] According to the National Comorbidity Survey Replication study, the lifetime prevalence of MDD is approximately 16 percent.[6] Risk factors for depression include female gender, younger age, family history of mood disorder, and personal history of mood disorder.[7,8] Women appear to be especially susceptible to depression, with a risk approximately two-fold greater than their male counterparts.[9] Unmarried marital status, unemployment, less than 12 years of education, and living in or near poverty have also been identified as risk factors for depression in Americans.[10]

Morbidity and Mortality

Major depression can be a particularly disabling psychiatric condition. The World Health Organization (WHO) has identified depression as a leading cause of disability and disease burden world-wide.[11] Individuals with depression may be at as much as a five-fold increased risk of disability.[12] In older individuals, depression is associated with increased risk of disability, impairment in activities of daily living, and decreased mobility.[13-16] The level of functional impairment associated with depression is comparable to or greater than disability associated with a number of medical disorders, including hypertension, diabetes, and arthritis.[17] A recent WHO survey found that depression was associated with the lowest overall health status among chronic medical conditions including asthma, angina, arthritis, and diabetes.[18]

In addition to profound effect on functional impairment and disability, depression is a significant risk factor for suicide-related mortality. The risk of suicide associated with depression varies across different populations of patients. In a meta-analysis of patients with depressive disorders, Bostwick and Pankratz found a "stair-step" progression in suicide risk based on treatment setting and the presence of specific suicidal thoughts or actions.[19] (see Figure 1.1). Patients treated in the outpatient setting had the lowest probability of suicide (2.2%), patients treated in the inpatient setting displayed a higher probability of suicide (4.0%), and inpatients admitted after a suicide attempt or with suicidal ideation had the highest probability for completed suicide (8.6%).

Figure 1.1 Lifetime risk of suicide for individuals with depression by treatment site and in the general population



Data from Bostwick and Pankratz,2000 [19]

Clinical Course

In over 70 percent of cases, depression is recurrent and episodic.[20] The incidence of depression increases rapidly in the mid-teens, after which the incidence rate is steady within a given age cohort.[20] The median age at onset of depression is in the mid-30s.[6] Left untreated, depression spontaneously remits in approximately 89 percent of individuals within two years.[21] If spontaneous remission of depression is to occur, it typically occurs in the first 3-4 months of the depressive episode. For those who do not remit in this timeframe, the chances of spontaneously remitting later are significantly lower.[21]

According to the American Psychiatric Association, treatment of depression is conceptualized as following three phases: acute, continuation, and maintenance.[22] The goal of the acute phase of treatment is to achieve remission of depressive symptoms. Remission is defined as a return to a baseline, pre-morbid level of symptom severity and global functioning. The period of time associated with the acute phase treatment of depression is patient-specific, but typically lasts 8-12 weeks.

Once remission of depression is achieved, continuation phase treatment is initiated. The purpose of continuation phase treatment is to prevent the return of depressive symptoms. Continuation phase treatment consists of continuing the treatment and dosage of medication that was successful in achieving remission for an additional 16-20 weeks.[22] Following successful continuation phase treatment and sustained remission of depressive symptoms, an individual is considered to have recovered from the initial episode of depression. A return of depressive symptoms during the continuation phase of treatment is considered a relapse.[23] The return of depressive symptoms after the completion of continuation treatment (i.e., after recovery) is considered recurrence.[23]

Recurrence is indicative of a new and separate episode of depression, distinct from the initial episode.

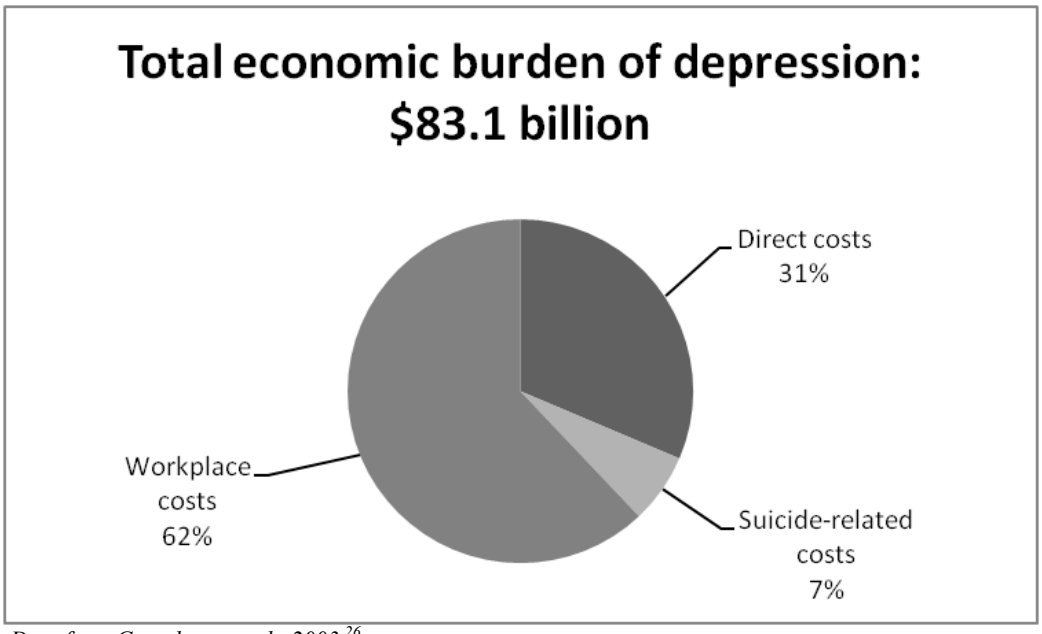
Recurrence rates are high among patients with a history of depression. Approximately one-half of individuals will experience a recurrent episode of depression after their first episode, and the risk of recurrence increases with each subsequent episode of depression.[24] By the time an individual has experienced three past episodes of depression, the probability of recurrence is 90 percent.[24] The presence of residual depressive symptoms is also associated with significantly increased risk of recurrent depression. An individual with residual depressive symptoms following acute treatment for depression has an approximately 3.5-fold increased risk for recurrent depression, and will relapse approximately 3 times faster than patients who achieve complete symptom remission.[25] For patients at high risk of recurrence, long-term maintenance phase treatment may be indicated. Factors which should be considered when determining the suitability of maintenance treatment for an individual include: the risk of recurrence, severity of previous episodes of depression, side effects experienced during treatment, and patient preference.[22] Maintenance phase treatment consists of long-term continuation of treatment with the primary objective of preventing future recurrence of depression.[22]

Economic Impact

The economic impact of depression is significant, and was estimated to amount to $83.1 billion dollars in 2000.[26] Much of the economic burden of depression is attributed to costs associated with workplace absenteeism and decreased workplace productivity. Of these costs, $51.5 billion were attributed to workplace costs, $26.1 billion to direct treatment costs, and $5.4 billion to suicide-related costs.[26] (see Figure 1.2). Druss et al.

found that patients with depression used, on average, a significantly greater number of sick days per year compared to patients with diabetes (9.86 vs. 7.17, p=0.04), heart disease (7.47, p=0.01), hypertension (5.39, p<0.001), or back problems (7.21, p=0.04).[27]

Figure 1.2 Total economic burden of depression, 2000



Data from Greenberg, et al., 2003 [26]

In addition to decreased productivity, individuals with major depression consume substantially greater healthcare resources than non-depressed patients. In a study of healthcare utilization among Canadians in Nova Scotia, patients with depression were 50 percent more likely to utilize a high amount of physician services, more likely to be hospitalized, have a hospitalization over three days, and have higher healthcare costs than non-depressed individuals.[28] Increased healthcare utilization translates into increased healthcare costs. Even after controlling for the influence of chronic medical conditions on

health care utilization, healthcare costs are higher among patients with depression compared to the non-depressed.[29]

Pathophysiology

The causes of depression are not well understood, but the etiology is likely complex and multi-factorial with genetics, environmental, and biological factors all contributing. Genetic factors are thought to account for approximately 40 percent of the risk for depression.[30,31] Studies indicate that depression tends to be familial,[32-35] with first degree family members of individuals with depression having an approximately three-fold increased risk for being diagnosed with depression.[30] Some research suggests that individuals who are at high familial risk for depression tend to have more severe and recurrent depression, with longer duration of depressive episodes, high levels of depression-related impairment, and recurrent thoughts of death or suicide.[36] Despite evidence of the genetic basis for affective disorders, researchers have been unsuccessful at identifying specific genes which confer risk. The reality of the heterogeneity and complexity of psychiatric disorders is such that it is unlikely that a single genetic risk factor will be isolated.[37] Rather, it is more likely that the genetic risk factors for depression are extremely complex, involving interactions between multiple genes, and interactions with environmental risk factors.[31]

The fundamental principle of biological psychiatry is that the physiological functioning of the human body and the brain can be used to explain the symptoms and experience of mental illness. Attempts have been made to "deconstruct" the symptoms associated with major depressive disorder and their associated neurophysiological circuits (See Table 1.1). A number of brain regions have been proposed to play a significant role

in the pathophysiology of depression including the prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus.[38]

Table 1.1 Hypothetical topography of symptoms of major depressive disorder.

Symptom(s)	Neural circuit(s)
Depressed mood and sadness	Medial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex
Sleep disturbances	Hypothalamic sleep-wake switch, brainstem sleep centers
Problems concentrating	Dorsolateral prefrontal cortex
Change in weight or appetite	Hypothalamus
Fatigue and anergia	Striatum, cerebellum, spinal cord
Anhedonia	Hypothalamus, nucleus accumbens
Feelings of worthlessness or guilt and thoughts of suicide	Amygdala, anterior cingulate cortex, medial prefrontal cortex, orbitofrontal cortex
Psychomotor agitation or retardation	Striatum, cerebellum

Adapted from Stahl, et al. [38]

While recent animal and human research has shed some light on potential brain regions involved in depression, historically much of what we know regarding the biological basis of depression is a result of the serendipitous discovery of pharmacological agents with effects on mood. In the 1950s and 1960s, researchers began to unravel the complex web of pharmacological, animal, and human clinical data describing the role of monoamines in mood disorders. Research uncovering the antidepressant activity of iproniazid and imipramine, as well as the potential for

medications such as reserpine and tetrabenazine to elicit depressive symptoms, resulted in initial formulation of the monoamine hypothesis of depression.[39]

The monoamine hypothesis of depression, as expressed in 1965 by Schildkraut, states that "depressions are associated with an absolute or relative decrease in cathecholamines, particularly norepinephrine, available at central adrenergic receptor sites. Elation, conversely, may be associated with an excess of such amines."[40] The monoamine hypothesis of depression as originally formulated was focused on the role of catecholamines, specifically norepinephrine, in the etiology of depression. Alec Coppen, publishing his review in the *British Journal of Psychiatry* two years after Schildkraut, argued for a role of serotonin in the etiology of depression.[41] In the 1970s, dopamine was added to the discussion of monoamines with potential relevance to depression.[39]

While the monoamine hypothesis of depression has an elegant and straightforward explanatory value (depletion of monoamines cause depression, restoration of monoamine levels corrects this deficiency and alleviates symptoms of depression), it is overly simplistic and does not account for a number of clinical observations. Most notably, the monoamine hypothesis does not adequately account for the observation that the onset of action of antidepressant medication is delayed over a period of weeks after starting treatment. While some treatment-emergent adverse effects such as nausea, irritability, and insomnia may appear acutely following administration of antidepressant medications, initial clinical resolution of depressive symptoms typically occurs over a prolonged period of time, typically two to four weeks.[22] This observation has led much of the current research to focus on potential mechanisms of action away from the synapse and actual monoamine levels, to distal sites of action. Some researchers have proposed that the delayed effectiveness of antidepressant medications may be due to

"time lag" related to gene expression and protein transcription at these distant sites of action.[31,42,43]

In addition to genetic and biological factors, non-genetic factors such as stress, traumatic life events, and environmental exposures are thought to be involved in the etiology of depression. The role of stress in the development of depression has garnered special attention. One of the mechanisms by which the human body responds to emotional or physical stress is by activation of the hypothalamic-pituitary-adrenal (HPA) axis.[43] HPA activation ultimately results in an increase in glucocorticoid secretion. In patients with depression, dysregulation of the HPA axis is thought to be related to alteration of glucocorticoid receptor expression and activity, and hypersecretion of corticotropin-releasing hormone.[44,45] Chronic hypercortisolemia may result in neural damage, especially in the areas of the brain such as the hippocampus and the amygdala which are associated with mood, cognition, and emotional regulation.[43]

Another area that has received recent attention is the role of neurotrophic factors in depression. Neurotropins are proteins that regulate the growth and differentiation of neural cells during development, as well as plasticity and survival of developed neuronal networks in the adult brain. Of particular interest is the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of depression. Via a number of different mechanisms, stress results in a reduction of BDNF in the central nervous system, and deficiencies of BDNF may play a role in central nervous system pathology, specifically in the hippocampus.[43] Interestingly, administration of antidepressant medication is associated with increased production of BDNF in the hippocampus.[46] Theoretically, an increase in BDNF production and other neurotrophins may have neuroprotective and neurorestorative effects, which may account for the therapeutic effects of antidepressant medications.[43,46]

Our understanding of the biological basis of depression is clearly limited. As researchers continue their quest to understand the genetic, biological and environmental factors involved in psychiatric mood disorders, their advances pave the way for novel pharmacological treatments for depression. Clinical research involving agents affecting the HPA axis, BDNF activity, and other biological targets are ongoing and may yield future novel treatments that not only improve the lives of individuals suffering from depression, but continue to enhance our understanding the complex biological mechanisms underlying depression.

Diagnosis

Depression is characterized by depressed mood and/or anhedonia occurring in the presence of a constellation of other symptoms including sleep changes, appetite changes, amotivation, anergia, impaired concentration, and feelings of guilt or worthlessness.[24] The Diagnostics and Statistical Manual-IV Text Revision (DSM-IV TR) is the gold standard in the United States for the diagnosis of mental disorders.[24] The DSM-IV TR criteria for major depressive disorder require the presence of five or more depressive symptoms, with either a depressed mood and/or anhedonia, being present (see Table 1.2).

It should be noted that diagnosis of depression is not based on objective diagnostic tests (e.g., blood chemistry, imaging, etc.). Rather, a diagnosis of depression is based on the presence of a collection of symptoms. As discussed previously, the underlying physiological activities that result in the symptoms associated with depression are likely diverse and heterogeneous across individuals. Therefore, what we characterize as depression is most appropriately conceptualized as a syndromatic umbrella under

Table 1.2 Diagnostic and Statistical Manual IV - Text Revision criteria for the diagnosis of Major Depressive Episode

A. Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful) (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others) (3) significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day (4) insomnia or hypersomnia nearly every day (5) psychomotor agitation or retardation nearly every day (6) fatigue or loss of energy nearly every day (7) feelings of worthlessness or excessive or inappropriate feelings of guilt nearly every day (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (9) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide B. Symptoms do not meet criteria for a Mixed Episode. C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. D. The symptoms are not due to the directy physiological effects of a substance, or a general medical condition. E. The symptoms are not better accounted for by Bereavement.

Adapted from American Psychiatric Association, 2000 [24]

which a variety of distinct or related pathophysiological processes fall. It is perhaps this complexity and heterogeneity that underlies the variable clinical presentation and unpredictable nature of treatment response in patients diagnosed with major depressive disorder.

Diagnostic Coding

According to the DSM-IV TR nosology, the diagnostic codes 296.2x and 296.3x are used to indicate a diagnosis of major depressive disorder (see Table 1.3). The DSM-IV TR code 311 may also be used to code depressive disorder, not otherwise specified.[24] For 296.2x and 296.3x, the fourth digit may be used to indicate whether the current episode of depression is the initial episode, or whether the current episode of depression is a recurrent episode (296.2x, single episode; 296.3x, recurrent). According to DSM-IV TR, an episode of MDD is considered to have ended when there exists a period of two months or more during which there is either complete resolution of depressive symptoms or depressive symptoms no longer meet the full diagnostic criteria. Note that the duration of sustained symptom remission indicative of recovery according to the DSM-IV TR differs from the APA treatment guidelines previously discussed. A return of depressive symptoms prior to a sustained two-month period of remission would be considered a relapse, and a continuation of the initial major depressive episode (coded as 296.2x). A return to syndromatic depression after sustained remission of depressive symptoms would be indicative of a recurrence of MDD, i.e., a new and distinct major depressive episode, and would be coded with DSM code 296.3x.

Table 1.3 Diagnostic and Statistical Manual IV - Text Revision diagnostic codes for major depressive disorder and related fourth and fifth digit specifiers

Code	Description
296.2x	Major Depressive Disorder, Single Episode
296.3x	Major Depressive Disorder, Recurrent
311	Depressive Disorder, Not Otherwise Specified
Fifth digit specifiers	
If full criteria for Major Depressive Disorder are met:	
296.x1	Mild
296.x2	Moderate
296.x3	Severe without psychotic features
296.x4	Severe with psychotics features
If full criteria for Major Depressive Disorder are NOT met:	
296.x5	In partial remission
296.x6	In full remission

In addition to the fourth digit codes, the DSM-IV TR coding schema allow for the use of a number of other specifiers to provide information about the psychiatric presentation of an individual with major depression (see Table 1.3). The DSM-IV TR fifth digit specifiers may be used to indicate either the current clinical status of an episode of depression or the severity of current presentation. If the individual meets the full diagnostic criteria for MDD at the time of assessment, the fifth digit is used to indicate the severity of the current episode. If the full diagnostic criteria for MDD are not met at the time of assessment, the fifth digit indicates the level of remission (i.e., in partial remission or in full remission). In addition to these specifiers captured in the diagnostic coding, the DSM-IV TR describes a number of other specifiers that are not coded. These specifiers include: chronic, with catatonic features, with melancholic features, with atypical features, and with postpartum onset. The International Statistical Classification

of Diseases and Related Health Problems, 9th revision clinical modification (ICD-9 CM) diagnostic codes for major depressive disorder correspond to the DSM-IV TR diagnostic codes.[47]

Treatment

Treatment Goals

The goals of treatment for depression are to achieve complete and sustained remission of depressive symptoms, complete functional recovery, and to prevent further episodes of depression.[22] Remission is defined as a return to premorbid normalcy, the complete absence of depressive symptoms, and the restoration of function.[48] Remission is distinct from treatment response in that response is, in practical terms, considered a significant but incomplete improvement in depressive symptomatology, whereas remission is the complete resolution of depressive symptoms. In clinical trials, treatment response is defined as a 50 percent reduction in the score of a depression-specific psychiatric rating scale.[48,49] In these studies, remission is defined in terms of a threshold score on the rating scale (e.g., 17-item Hamilton Depression Rating Scale score < 7).[48,49]

In clinical practice patient-rated assessments of depression severity, such as the 9-item Patient Health Questionnaire (PHQ-9), may be used to assess and track the severity of depression during the course of treatment.[50] The PHQ-9 is derivative from the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire instrument.[51] The PHQ-9 consists of the 9 items from the depression module of the broader Patient Health Questionnaire.[50,51] Each item included in the PHQ-9 is tied to one of the DSM-IV criteria for depression. Patients are asked to score each item based on the frequency of experiencing specific symptoms within the past 2 weeks (scoring: 0, not at

all; 1, several days; 2, more than half the days; 3, nearly every day). Therefore, PHQ-9 scores range from 0-27, with higher scores indicating increasing severity of depression symptoms. Breakpoints for interpreting PHQ-9 scores are provided in Table 1.4.

Table 1.4 Interpretation of Patient Health Questionnaire-9 scores

PHQ-9 score	Depression severity
1 to 4	None
5 to 9	Mild
10 to 14	Moderate
15 to 19	Moderately Severe
20 to 27	Severe

Adapted from Kroenke et al., 2001 [50]

Pharmacotherapy

The discovery of the antidepressant effects of iproniazid and imipramine, along with the discovery of the antipsychotic chlorpromazine, marked the advent of modern psychopharmacology. Imipramine and iproniazid were the unexpected result of unrelated research on antihistamine and anti-tubercular agents, respectively.[39] Following the discovery of the antidepressant effects of these agents, a number of related medication therapies were developed, giving rise to the monoamine oxidase inhibitors (MAOIs) and the other tricyclic antidepressants (TCAs). Despite their effectiveness as antidepressant agents, these early agents were plagued by poor tolerability and safety concerns. The MAOIs interact with many other medications as well as some food products to cause a hypertensive reaction, while the TCAs are associated with significant adverse effects, cardiovascular toxicity, and can be lethal in overdose situations.[52-54] Based on an

understanding of the pharmacodynamics of these early antidepressant medications, a number of novel compounds were developed beginning in the late 1970s and early 1980s. These novel compounds include the selective serotonin reuptake inhibitors, the serotonin-norepinephrine reuptake inhibitors, as well as a number of other agents. While these newer medications have a more favorable tolerability and safety profile than the older agents, no significant advances in terms of antidepressant effectiveness have been made.[55]

Antidepressant therapy is the mainstay of medication treatment for depression. A number of medication alternatives are available for the treatment of depression; the most commonly used medications currently include: Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and the atypical antidepressants (bupropion, mirtazapine) (see Table 1.5). These medications are considered equally effective for the treatment of uncomplicated major depression; however, they differ greatly with regards to their safety and tolerability profiles.[22] The SSRIs are the most commonly prescribed class of antidepressant medication in the United States, likely due to their favorable safety and tolerability profile. In addition to efficacy as antidepressant treatments, these medications are used in a variety of other psychiatric conditions, including anxiety disorders.

Table 1.5 Classification of commonly used antidepressant agents

Generic name	Brand name
SSRIs	
Fluoxetine	Prozac®
Sertraline	Zoloft®
Paroxetine	Paxil®, Paxil CR®, Pexeva ®
Citalopram	Celexa®
Escitalopram	Lexapro®
Fluvoxamine	Luvox®, Luvox CR®
SNRIs	
Venlafaxine	Effexor®, Effexor XR®
Duloxetine	Cymbalta®
Desvenlafaxine	Pristiq®
Atypical Antidepressants	
Bupropion	Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®
Mirtazapine	Remeron®
Tricyclic Antidepressants	
Amitriptyline	Elavil®
Clomipramine	Anafranil®
Desipramine	Norpramin®
Doxepin	Sinequan®
Imipramine	Tofranil®
Nortriptyline	Pamelor®
Protriptyline	Vivactil®
Trimipramine	Surmontil®

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant

The mechanism of action for each of the modern antidepressant medications varies by class. All U.S. Food and Drug Administration (FDA)-approved antidepressant medications act either directly or indirectly on monoamine neurotransmission. The SSRI antidepressants are so named due to their selective inhibition of the serotonin reuptake transport protein located on presynaptic neurons.[56] The most commonly prescribed SSRI antidepressants for depression are fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. SNRI medications exert their action by inhibiting the activity of both serotonin and norepinephrine reuptake transport proteins.[57] FDA-approved SNRI medications include venlafaxine, duloxetine and desvenlafaxine. The TCA medications exert their antidepressant effect by inhibiting norepinephrine and serotonin reuptake to extents that vary according to the pharmacodynamic profile of each individual tricyclic agent.[58] The antidepressant medication bupropion is thought to exert its antidepressant activity through its affinity for norepinephrine and dopamine transport proteins; however, bupropion displays a relatively low affinity for the serotonin transport protein.[59] This unique mechanism of action is thought to explain the side effect profile of bupropion, with relatively low rates of sexual dysfunction reported during treatment.[60] The antidepressant medication mirtazapine has a complex mechanism of action whereby it increases noradrenergic and serotonergic neurotransmission indirectly by blocking presynaptic α_2 receptors. Simultaneous to α_2 blockade, mirtazapine alters neurotransmitter activity at the level of postsynaptic receptors by blocking 5-HT_2 and 5-HT_3 receptors.[61]

Of particular interest to clinicians is how to best utilize the wide variety of antidepressant medications available for the treatment of depression. A number of organizations have released evidence-based consensus guidelines and treatment algorithms to inform clinical decision making in the treatment of depression.[22,62] The Texas Medication Algorithm Project treatment guidelines recommend a stepwise

approach to treatment of depression, beginning with antidepressant monotherapy and branching to a variety of augmentation and switch strategies as the individual clinical situation dictates.[62] Results from the STAR*D effectiveness study indicate that if a sequential algorithm for the treatment of depression is optimally implemented, remission rates of up to 70 percent are achievable.[63]

Summary

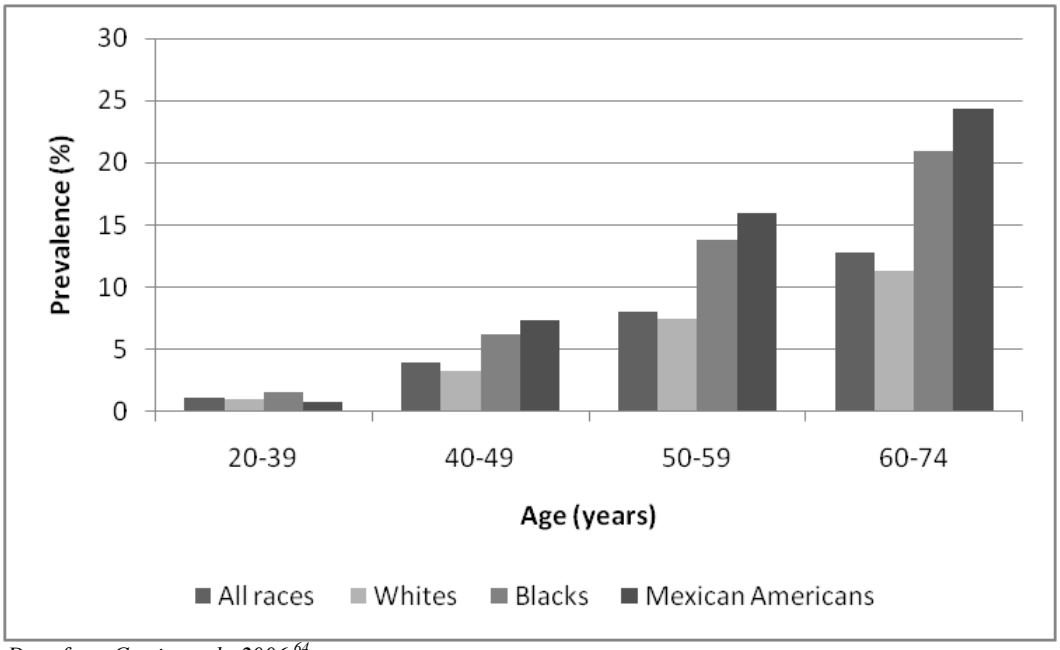
Depression is a serious and debilitating mental illness that affects a significant number of Americans. The course of depression is typically chronic and recurrent. Depression is associated with significant morbidity, mortality, and economic costs. The biological phenomena underlying depression are not completely understood, but depression is thought to be related to a combination of genetic, biological, and environmental factors. A number of medications including SSRIs, SNRIs, and other antidepressant medications have demonstrated efficacy for the treatment of depression. Remission is the goal of treatment for depression, and is associated with improved functioning and decreased risk for recurrence of depression. Remission is achieved by approximately one-third of subjects in acute treatment trials with antidepressant medications. Sequential treatment strategies based on evidence-based algorithms may increase remission rates to as high as two-thirds.

DIABETES MELLITUS

Epidemiology

Diabetes mellitus (DM, referred to simply as diabetes hereafter) is an endocrine disorder characterized by impaired glycemic control and hyperglycemia. According to National Health and Nutrition Examination Survey (NHANES) data from 1999-2000, the prevalence of diabetes in the United States is just over 9 percent, and affects nearly 20 million Americans.[64] The prevalence of diagnosed diabetes increases with older age and varies by race (see Figure 1.3). Diagnosed diabetes is more common among non-Hispanic blacks (11.0%) and Mexican-Americans (10.4%), with prevalence among these ethnicities approximately two-fold higher than that of non-Hispanic whites (5.2%).[64] Of particular concern, 2.8 percent of Americans have undiagnosed diabetes.[64] Also alarming is the high overall prevalence of impaired fasting glucose (26.0%), indicating that a significant number of Americans are at high risk for development of diabetes and for cardiovascular disease. [64]

Figure 1.3 Prevalence of diagnosed diabetes mellitus by age and race



Data from Cowie et al., 2006 [64]

Risk factors for diabetes and prediabetes are summarized in Table 1.6. The risk of type 2 diabetes increases with age and lack of physical activity.[65] Diabetes is also more common among people with a family history of diabetes, and women with a history of gestational diabetes.[65] Obesity is a well recognized risk factor for diabetes, increasing risk over seven-fold.[66] The prevalence of diabetes, as discussed earlier, is higher among certain ethnic groups. Specifically, Hispanic, non-Hispanic black, Asian American, Native American, or Pacific Islander ethnicities are considered a risk factor for diabetes.[65] Individuals with hypertension, dyslipidemia, cardiovascular disease, and a history of impaired fasting blood glucose or impaired glucose tolerance are also at an increased risk for later developing diabetes.[65] Exposure to certain medications, such as atypical antipsychotics[67] and corticosteroids,[68] may increase the risk of hyperglycemia and

diabetes. Polycystic ovarian syndrome and psychiatric illness are other recognized risk factors for diabetes mellitus.[65]

Table 1.6 Risk factors for diabetes and prediabetes

Risk Factors
Family history of diabetes
Cardiovascular disease
Overweight or obesity
Sedentary lifestyle
Hispanic, non-Hispanic black, Asian American, Native American, or Pacific Islander ethnicity
Impaired glucose tolerance or impaired fasting glucose
Hypertension
Dyslipidemia
History of gestational diabetes
Polycystic ovary syndrome
Psychiatric illness

Adapted from Rodbard et al., 2007 [65]

Classification

Diabetes can be classified into four types: Type 1, Type 2, gestational, or diabetes due to other causes (e.g., drug induced).[69] Type 1 diabetes mellitus (T1DM) accounts for 5-10 percent of all cases of diabetes, is characterized by the complete absence of insulin production, and is thought to be the result of an autoimmune response resulting in destruction of the insulin-producing beta cells in the pancreas.[65,69] Type 2 diabetes mellitus (T2DM) is a complex metabolic condition thought to be related to decreased physiological sensitivity to insulin, decreased insulin production, and/or increased hepatic glucose production.[65,69] Type 2 diabetes accounts for approximately 90-95 percent of all cases of diabetes.[69] Gestational diabetes mellitus is characterized by glucose intolerance

with onset during pregnancy, and affects approximately 4 percent of all pregnancies.[69] Diabetes may also be associated with a number of other specific causes, including medications and other medical conditions. In recent years, the American Diabetes Association has also recognized the category of "pre-diabetes."[69] Individuals who meet criteria for pre-diabetes are at high risk for developing diabetes.[65,69]

Pathophysiology

Diabetes is associated with hyperglycemia due to reduced production of insulin, a decrease in insulin's physiological effects, increased hepatic glucose production, or a combination of these factors. The etiology of diabetes is multi-factorial in nature, influenced by both genetic and environmental factors. While development of T1DM is not genetically predestined, genetic factors can increase risk of developing this condition. Human leukocyte antigen (HLA) DR and HLA-DQ appear to have a strong association with diabetes[69], with other HLA components likely playing a significant role as well.[70] Autoimmune destruction of the insulin-producing beta cells of the pancreas leads to insulin deficiency, hyperglycemia, and the hallmark characteristics of diabetes. Autoimmune antibodies indicative of this process are present in up to 90% of individuals with T1DM.[69]

The etiology of T2DM is fundamentally related to pathological changes in insulin secretion and activity, and hepatic production of glucose.[65] Adiposity plays a pivotal role in the development of T2DM. Increases in adiposity lead to decreases in sensitivity to insulin and increased circulating glucose levels.[65] This hyperglycemia leads to further insulin desensitization and increased insulin production, perpetuating a cycle of insulin resistance and increased production, compounding the problem of glycemic

dysregulation. Ultimately, repeat hyperglycemia, as well as the actions of cytokines, leptin, and dyslipidemia result in pancreatic beta cell burn-out.[71]

Diagnosis

Diabetes can be diagnosed by fasting blood glucose (FBG), causal blood glucose measurement, or by oral glucose tolerance test (OGTT) .[65,69] The diagnostic criteria must be met on two separate occasions, on different days, in order for a diagnosis of diabetes to be made.[69] In a broadening of the concept of glycemic abnormalities, the category of pre-diabetes was introduced in 2003 by the American Diabetes Association. Pre-diabetes is identified by the presence of either an impaired FBG or an impaired OGTT, and is a risk factor for the development of diabetes and future cardiovascular disease.[69] The American Diabetes Association criteria for diagnosis of diabetes and pre-diabetes are presented in Table 1.7.

Table 1.7 American Diabetes Association diagnostic criteria for diabetes mellitus

Diagnosis	Criteria
Diabetes	FBG ≥ 126mg/dl
	Casual BG > 200mg/dl and symptoms of hyperglycemia
	2-h post OGTT plasma glucose level ≥ 200mg/dl
Pre-diabetes	FBG 100-125 mg/dl
	2-h post OGTT plasma glucose level 140-199 mg/dl

FBG, fasting blood glucose; OGTT, oral glucose tolerance test

Diagnostic Coding

The ICD-9 CM codes 250.0x to 250.9x are used to code diabetes (see Table 1.8).[47] The ICD-9 CM code 250.0 is used to indicate a diagnosis of diabetes mellitus without further specification for the presence of complications or classification. The ICD-9 CM fourth digit may be used to indicate the presence of diabetic complications including ketoacidosis (250.1), renal complications (250.4), and ophthalmic complications (250.5). A fifth digit code may be used to identify the particular classification of diabetes (i.e., type 1 vs. type 2) and the level of glycemic control (controlled or uncontrolled).

Table 1.8 International Statistical Classification of Diseases and Related Health Problems, 9th Revision clinical modification codes for diabetes and related disorders

ICD-9 CM code	Description
Diabetes codes	
250.0	Diabetes mellitus without mention of complication
250.1	Diabetes with ketoacidosis
250.2	Diabetes with hyperosmolarity
250.3	Diabetes with other coma
250.4	Diabetes with renal manifestations
250.5	Diabetes with ophthalmic manifestations
250.6	Diabetes with neurological manifestations
250.7	Diabetes with peripheral circulatory disorders
250.8	Diabetes with other specified manifestations
250.9	Diabetes with unspecified complication
250.x0	Diabetes mellitus type 2 or unspecified type
250.x1	Diabetes mellitus type 1
250.x2	Diabetes mellitus type 2 or unspecified type, uncontrolled
250.x3	Diabetes mellitus type 1, uncontrolled
Other related codes	
251.0	Hypoglycemic coma
251.1	Other specified hypoglycemia
251.2	Hypoglycemia unspecified
277.7	Dysmetabolic syndrome x
362.0x	Diabetic retinopathy*
366.41	Diabetic cataract
357.2	Polyneuropathy in diabetes
585.x	Chronic kidney disease

*added in 2006

Treatment

Treatment Goals

The goals of treatment for diabetes are to effectively manage glycemic control and to prevent complications associated with diabetes. Glycemic control is evaluated in terms of FBG and glycosylated hemoglobin (hemoglobin A1c or HbA1c). Fasting blood glucose values indicate a "snapshot" of an individual's glucose level at a moment in time, whereas HbA1c levels reflect the average glycemic levels over a period of time approximating 120 days.[72] According to the American Diabetes Association guidelines, HbA1c is the primary target for glycemic control and the lab test should be obtained initially and routinely during the course of care.[73] In order to make the concept of HbA1c easier for patients to integrate into their self-monitoring practices, the American Diabetes Association has recommended the use of the term estimated average glucose (eAG) to express the equivalence between HbA1c and mean plasma glucose levels.[73] (see Table 1.9). In addition to having utility for evaluating glycemic control over a period of months, HbA1c has also been shown to be predictive of diabetic complications and outcomes associated with chronic diabetes.[74]

A summary of the American Diabetes Association recommendations for achieving glycemic control in adults with diabetes is presented in Table 1.10.[73] Notably, while the American Diabetes Association indicates that the target HbA1c for patients with diabetes should be < 7 percent, other organizations recommend more aggressive targets for HbA1c. The American Association of Clinical Endocrinologists recommends a target HbA1c of < 6.5 percent for patients with diabetes.[65]

Table 1.9 Relationship between hemoglobin A1c level and estimated average glucose.

HbA1c value (%)	eAG (mg/dl)
6.0	126
7.0	154
8.0	183
9.0	212
10.0	240
11.0	269
12.0	298

HbA1c, hemoglobin A1c; eAG, estimated average glucose

Adapted from American Diabetes Association, 2009 [73]

Table 1.10 Summary of American Diabetes Association glycemic goals for adults with diabetes

Assessment	Goal
HbA1c	< 7.0%
Pre-prandial plasma glucose	70-130 mg/dl
Peak post-prandial plasma glucose	< 180 mg/dl

Adapted from Stratton, 2000 [73]

Non-pharmacological Treatment

Successful management of diabetes typically requires both lifestyle interventions as well as medication treatment. The American Diabetes Association recommends that any treatment plan for diabetes incorporates diabetes self-management education including instruction for proper self-monitoring of blood glucose (SMBG) and education on medical nutritional therapy.[73] Self-monitoring of blood glucose can be used to evaluate the effectiveness of medication treatment and to prevent hyper- and hypoglycemia.[73] Self-monitoring allows patients to monitor their level of glycemic control on an ongoing basis, is useful to inform treatment decisions, and may help in preventing hypoglycemia.[73] In patients with diabetes receiving insulin treatment, SMBG

is especially important, and the American Diabetes Association recommends SMBG at least three times daily for these patients.[73] Self-monitoring of blood glucose may be useful, as well, in patients with T2DM not receiving insulin treatment. Research suggests that SMBG is associated with a reduction of 0.4 percent in HbA1c when SMBG is included in the treatment plan of individuals with T2DM.[75]

Medical nutrition therapy (MNT) is the primary non-pharmacological therapy for the treatment, prevention, and control of diabetes.[65,73,76] The goal of MNT is to reduce the risk of diabetes and cardiovascular disease through nutritional choices and physical activity. Specifically, the goals of MNT are to achieve glycemic control within the normal range, to achieve a lipid profile that reduces cardiovascular risk, to maintain blood pressure control, to prevent or slow the development of diabetic complications, and to address nutritional needs.[76] Research indicate that MNT can have a profound impact on glycemic control, reducing HbA1c by 1-2 percent.[77] MNT is also effective for preventing the development of diabetes in individuals at high risk for the disease.[77]

Pharmacological Treatment

Medication treatment for diabetes varies according to the classification of diabetes. Due the lack of insulin production characteristic of T1DM, medication treatment for T1DM consists of insulin replacement therapy.[65,69] The American Diabetes Association recommends a general insulin replacement strategy consisting of multiple daily dosage of basal and prandial insulin, or continuous subcutaneous insulin infusion (insulin pump therapy).[73] A variety of human insulin formulations have been developed to optimally mimic the normal physiological profile of insulin and to achieve glycemic control (see Table 1.11).

Table 1.11 Insulin formulations used for the treatment of diabetes mellitus

Insulin Formulation	Onset	Peak	Duration
Rapid-acting			
Insulin aspart	5-15 min	1-2 h	3-5 h
Insulin lispro	5-15 min	1-2 h	3-4 h
Insulin glulisine	5-15 min	1-2 h	3-4 h
Short-acting			
Regular	30-60 min	2-3 h	3-6 h
Intermediate, basal			
NPH	2-4 h	4-6 h	8-12 h
Lente	3-4 h	6-12 h	12-18 h
Long-acting, basal			
Insulin ultralente	6-10 h	10-16 h	18-20 h
Insulin glargine	4-5 h	N/A	22-24 h

Adapted from Dipiro et al. [78]

Medication treatment for T2DM consists of oral antidiabetic agents, injectable antidiabetic agents, and insulin replacement therapy. Selection of specific treatment for T2DM is guided by consideration of the glycemic effects, non-glycemic effects, safety and tolerability, and ease of use of the individual agents.[79] Five classes of oral antidiabetic medications are available for the treatment of T2DM: sulfonylureas (SU), meglitinides, biguanides, thiazolidinediones (TZD), and alpha-glucosidase inhibitors. Examples of each of these medication classes are provided in Table 1.12. A number of combination formulations of these agents are also available (see Table 1.13).

Table 1.12 Oral antidiabetic medications for the treatment of type 2 diabetes mellitus

Medication	Initial Dosage	Maximum Dosage	Mechanism of action
Sulfonylureas			Stimulate insulin release. Administered once daily.
Glyburide	1.25-5 mg/day	20 mg/day	
Glipizide	2.5-5 mg/day	40 mg/day	
Glimepiride	1-2 mg/day	8 mg/day	
Meglitinides			Stimulate insulin secretion. Short acting agents adminstered 15-30 minutes before each meal.
Repaglinide	0.5mg TID	16 mg/day	
Nateglinide	60-120 mg TID	360 mg/day	
Biguanides			Inhibit hepatic glucose production. First line agent for T2DM.
Metformin	500-850 mg/day	2550 mg/day	
Thiazolidinediones			Increase insulin sensitivity.
Pioglitazone	15-30 mg/day	45 mg/day	
Rosiglitazone	4 mg/day	8 mg/day	
DPP inhibitors			Potentiate incretin effects.
Sitagliptin			
Alpha-glucosidase inhibitors			Delay carbohydrate absorption, decreasing post-prandial hyperglycemia.
Acarbose	25mg TID	300 mg/day	
Miglitol	25 mg TID	300 mg/day	

Table 1.13 Combination oral antidiabetic medications for the treatment of type 2 diabetes mellitus

Medication	Available Dosages	Maximum Dosage
Metformin + pioglitazone	500mg/15mg 800mg/15mg	2550mg/45mg per day
Metformin + rosiglitazone	500mg/1mg 500mg/2mg 500mg/4mg 1000mg/2mg 1000mg/4mg	2000mg/8mg per day
Metformin + glyburide	250mg/1.25mg 500mg/2.5mg 500mg/5mg	2000mg/20mg per day
Metformin + glipizide	250mg/2.5mg 500mg/5mg 500mg/5mg	2000mg/20mg per day
Metformin + repaglinide	500mg/1mg 500mg/1mg	2500mg/10mg
Metformin + sitagliptin	500mg/50mg 1000mg/50mg	2000mg/100mg per day
Rosiglitazone + glimepiride	4mg/1mg 4mg/2mg 4mg/4mg 8mg/2mg 8mg/4mg	8mg/4mg per day

The comparative effectiveness and safety of oral hypoglycemic medications for the treatment of type 2 diabetes was evaluated systematically by Bolen and colleagues.[80] They reviewed clinical data from 216 trials and 2 systematic reviews involving oral hypoglycemic medications and performed a variety of assessments of comparative effectiveness (including control of HbA1c, blood pressure, and lipid levels) and safety (hypoglycemia and other adverse events). In light of the lack of substantial clinical research involving other agents, analyses and conclusions focused primarily on comparisons of metformin, SUs, and TZDs. In terms of glycemic control, monotherapy with TZDs, second generation SUs, and metformin was associated with similar absolute reductions in HbA1c of approximately 1 percent. Combination hypoglycemic treatment (metformin + TZD, metformin + SU, or SU + TZD) was more effective than monotherapy, and was associated with approximately a 1 percent reduction in HbA1c over monotherapy. The absolute effect of all oral hypoglycemic medications on blood pressure was minimal, and there were no statistically significant differences found between any of the treatments. In terms of low density lipoprotein (LDL) cholesterol, metformin was associated with a 10 mg/dL decrease, TZDs were associated with a 10 mg/dL increase, and SUs had minimal effect on LDL levels. Thiazolidinediones, either in combination or monotherapy, were associated with an increase in high density lipoprotein (HDL) cholesterol of 3-5 mg/dL, while SUs and metformin had no effect on HDL levels. In terms of safety, hypoglycemia was more common with SUs, while gastrointestinal disturbances were more common with metformin. Higher risk for edema was associated with TZDs compared to metformin and SUs.

Individuals typically begin treatment for T2DM with lifestyle intervention and medication monotherapy. Medication treatment may progress to combination therapy if necessary, based on response to initial treatment. The American Diabetes Association

recommends initiation of metformin in addition to lifestyle interventions for initial treatment of type 2 diabetes.[79] If an individual is unable to achieve or maintain adequate glycemic control with metformin monotherapy, the American Diabetes Association recommends that augmentation with either an SU or basal insulin should be implemented within a period of 2-3 months. If combination oral treatment (metformin + SU) is not able to achieve glycemic control, than combination treatment with metformin + insulin is indicated. Alternatively, second-tier treatment strategies with less evidence include other two-drug combinations (i.e., metformin + pioglitazone or metformin + exenatide) and may be preferred in certain patients. Triple combination oral treatment (metformin + pioglitazone + SU) may also be considered in some patients.

Medication-taking Behaviors in Patients with Diabetes

Medication-taking can be particularly challenging for individuals with diabetes. A number of retrospective and prospective studies have evaluated medication-taking behaviors in diabetic patients, and attempted to identify barriers to optimal medication adherence. While no studies have specifically evaluated antidepressant medication-taking behavior among patients with diabetes, significant research has been conducted evaluating antidiabetic medication adherence and persistence among patients with diabetes.[81-100] Key components and findings of these studies are summarized in Appendix A.

Antidiabetic medication adherence in patients with diabetes may be affected by the complexity of the medication regimens involved, the cost of treatment, emotional well-being, as well as knowledge about the disease state and medication.[101] Additionally, a number of barriers unique to insulin treatment, such as fear of needles, inconvenience, and physician resistance have been identified.[102] In medication adherence studies involving patients with diabetes on oral antidiabetic medication treatment, age, gender, medication factors, medication regimen complexity, medical comorbidity, and psychological factors have all been associated with diabetic medication non-adherence.[81,84-86,88,89,92,96,99,100] These findings are summarized in Table 1.15.

Table 1.14 Factors associated with antidiabetic medication non-adherence in studies using pharmacy claims data

Author, year	n	Medications studied	Factors associated with nonadherence
Venturini, 1999	786	SU	Age Medication class Number of daily doses of medication Self-reported compliance New start vs. continuing treatment
Dailey, 2002	23400	ODM and/or insulin	Polytherapy
Dezii, 2002	992	Glipizide	Younger age Dosage regimen
Donnan, 2002	2849	SU or MET	SU: Age Daily number of tablets No. of other medications Social Deprivation MET: No. of other medications
Mellkian, 2002	1815	SU+MET	Age >55 Total nubmer of tablets per day
Morningstar, 2002	3358	SU or MET	Age Gender Drug class Days in hospital
Balkrishnan, 2003	775	ODM, insulin, or combination	Use of insulin or combination ER visit in preceding year Higher Charlson comorbidity score
Hertz, 2005	6090	SU, MET, MEG, TZD, AGI, insulin	Adherence: Age Hypertenstion Dyslipidemia Average number of rx Non-persistence: Age Gender Drug class History of Depression Type of insurance plan Average number of rx (neg assn)
Adams, 2008	1806	oral hypoglycemics	Black ethnicity
Rozenfeld, 2008	2741	SU, MET, AGI, TZD, MEG	Younger age Lower chronic disease score Lower medication burden

n, number of subjects; SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; MEG, meglidinide ; ODM, any oral diabetic medication

A high level of adherence to antidiabetic medication treatment is essential to achieving optimal medical outcomes. A number of studies have evaluated the clinical and economic outcomes associated with poor adherence to pharmacological treatment of diabetes (see Appendix B).[90,95,97,99,100,103,104] While most studies have utilized the medication possession ratio (MPR) or a similar calculation to measure medication adherence,[90,95,97,99,100] two prospective studies utilized patient self-report or the 4-item Morisky survey to evaluate medication adherence.[103,104]

Higher level of adherence to oral antidiabetic medication treatment is consistently associated with improved glycemic control. In retrospective studies, the relationship between medication adherence and glycemic control is consistently inverse,[90,95,97,99,100] with a modest magnitude (a 10 percent increase in medication adherence is associated with a 0.1-0.14 percent absolute reduction in HbA1c).[90,95,100] In an evaluation involving 810 indigent care patients, Schectman et al. found that a 10 percent increase in medication adherence was associated with an absolute reduction in HbA1c of 0.16 percent.[90] Improved metabolic control was associated with increased age, White race/ethnicity, and medication adherence. Pladevall et al. found a similar relationship between medication adherence and glycemic control in their retrospective evaluation of pharmacy claims and medical clinic data.[95] Among 677 subjects with T2DM, they found that a 10 percent decrease in medical adherence was associated with an absolute increase in HbA1c of 0.14 percent. Rozenfeld et al. reinforced the apparent relationship and magnitude of the association between medication adherence and HbA1c, reporting that a 10 percent increase in medication adherence was associated with a 0.1 percent absolute decrease in HbA1c in their retrospective evaluation.[100] While the magnitude of the relationship between antidiabetic medication adherence and HbA1c may appear numerically modest, evidence suggests that a decrease in HbA1c of any magnitude is

associated with a clinically significant reduction in risk for clinical complications of diabetes.[74]

In studies evaluating antidiabetic medication adherence via patient self-report, the association between medication adherence and glycemic control is not as consistent as in studies using objective measures. While some studies suggest a negative association between adherence and HbA1c,[103,104] other earlier studies have not found an association between self-reported medication adherence and glycemic control.[105-108] Patient self-report may not be a valid or reliable measure of actual medication adherence. Indeed, an analysis comparing an electronic measure of medication adherence (MEMS cap), patient self-reported adherence, and physician-reported adherence for a sample of diabetic patients receiving treatment found that both patient- and physician-reported medication adherence was much higher compared to the electronic measure of medication adherence.[109] Similar trends in medication adherence assessment have been reported in a variety of other chronic disease states.[110-113]

A number of studies have evaluated the associations between antidiabetic medication adherence and economic and service utilization outcomes (See Table 1.17).[92,94,98,114] Research suggests that poor diabetic medication adherence is associated with increased risk of hospitalization and increased mortality rates. In a study involving data for 11,532 patients with diabetes, Ho et al. found that poor diabetic medication adherence was associated with increased HbA1c, as well as increased rates of all-cause hospitalization and all-cause mortality.[98] Likewise, Lau et al. found that the odds of hospitalization was over 2-fold higher for subjects non-adherent to their diabetic medications compared to those who were adherent.[94] While poor adherence is associated with increased service utilization, the economic consequences associated with poor diabetic medication adherence are not clear. Balkrishnan et al. found that a 10 percent

increase in MPR was associated with an 8.6 percent decrease in total healthcare costs, while other research suggests that medical care cost-savings associated with medication adherence may be offset by increased medication-related costs.[92] In a study involving 57,687 patients with diabetes, Hepke et al. found that lower rates of medication adherence was associated with increased emergency department visits and increased medical care costs; however, from the perspective of the managed care organization, total healthcare costs were unaffected due to increased medication costs.[114]

Table 1.15 Studies evaluating the relationship between antidiabetic medication adherence and economic and service utilization outcomes for patients with diabetes

Author, year	n	Design	Outcomes Evaluated	Findings
Balkrishnan, 2003	775	Prospective cohort	Total healthcare costs	10% increase in MPR associated with 8.6% decrease in total annual healthcare costs ($p<0.001$)
Hepke, 2004	775	Retrospective cohort	Total healthcare costs, use of ED services, inpatient admission	Increased levels of medication adherence associated with increased total healthcare costs and decreased ED utilization.
Lau, 2004	900	Retrospective cohort	DM or CVD-related hospitalizaion	Increased risk of hospitalization (OR 2.53) with poor ODM adherence (MPR <80%).
Ho, 2007	11532	Retrospective cohort	All-cause hospitalization, all-cause mortality	Medication non-adherence was associated with increased risk for all-cause hospitalization (OR 1.38) and all-cause mortality (OR 1.39). A 25% increase in adherence associated with 0.05% reduction in HbA1c.

n, number of subjects; MPR, medication possession ratio; ED, emergency department; DM, diabetes mellitus; CVD,cardiovascular disease; OR, odds ratio; ODM, oral diabetic medication

Summary

Diabetes is an endocrine disorder affecting nearly 20 million Americans, a significant number of who may be undiagnosed. Diabetes and complications associated with diabetes result in significant morbidity and mortality and related economic costs. The mainstay of treatment for type 1 diabetes mellitus is insulin replacement therapy. For patients with type 2 diabetes mellitus, oral antidiabetic medications are first-line treatments. Regardless of the type of diabetes, diabetes self-management education, lifestyle interventions, and medical nutrition therapy are essential facets of diabetes management. While a number of medications have demonstrated effectiveness for the treatment of diabetes, barriers such as poor medication adherence remain a significant obstacle. Medication non-adherence in patients with diabetes is associated with poor glycemic control, increased healthcare services utilization, and increased morbidity and mortality.

COMORBID DIABETES MELLITUS AND MAJOR DEPRESSIVE DISORDER

Epidemiology

In studies evaluating the prevalence of depression among diabetic patients, the estimated prevalence of depression ranges from 3.8 percent to 60.7 percent, with an aggregate prevalence of 25.3 percent.[115] These estimates appear to be influenced by a number of factors, including gender, the type of diabetes, the method used to evaluate depression, as well as the site of recruitment for epidemiology study participants. In individuals with diabetes the prevalence of depression is higher among women than men (28% vs. 18%), and among patients with T2DM compared to those with T1DM (27% vs. 21%). Patients evaluated with self-reported symptom questionnaires report a higher prevalence of elevated depressive symptoms compared to those evaluated with a standardized diagnostic interview (31% vs. 11%). This is likely due to the limited specificity of self-report measures of depression (i.e., these instruments may pick up symptoms unrelated to depression, but related to some other disorder). Recruitment site also appears to effect prevalence estimates, with patients recruited from clinical settings displaying higher rates of depression compared to subjects recruited from the community (32% vs. 20%).

While prevalence estimates vary greatly across the previously discussed factors, the ratio of the odds for experiencing depression with comorbid diabetes to the odds of depression among non-diabetics is relatively stable across these factors.[115] Overall, the odds of experiencing depression are approximately two-fold higher for individuals with diabetes compared to non-diabetics, and the odds ratio appears consistent across gender, diabetes type, community- vs. clinic-based sampling, or the assessment method utilized. This seems to indicate that the risk factors for depression in diabetes are similar to the

risk factors for depression among non-diabetic patients; however, the presence of depression magnifies the effect of these risk factors two-fold. In light of the high prevalence of depression among patients with diabetes and the profound implications that depression can have on the clinical course of diabetes, the high rate of undiagnosed depression in this population is particularly worrisome. It has been estimated that up to two-thirds of patients with diabetes and comorbid depression have their mood disorder go undiagnosed and untreated.[116]

Scarce research has evaluated the epidemiology of depression and comorbid diabetes in underserved populations. Research from the early 1990s found no increased prevalence of depression among Hispanic men or women with diabetes, when compared to those without diabetes.[117] Other research by Black et al. found a high prevalence of depressive symptoms among a sample of older Hispanic patients, and the prevalence was higher among subjects with diabetes compared to those without diabetes (31% vs. 24%).[118] The presence of significant depressive symptoms in this study was also associated with significant risk for diabetic complications, functional disability, and greater health service use. In a cross-sectional study of 209 Hispanics with diabetes, 33.5 percent had comorbid depression.[119] Subjects with moderate to severe depression were more likely to be younger in age, female, and living alone, when compared to their non-depressed counterparts. In a community-based sample of 126 Hispanic women receiving treatment for diabetes, the prevalence of depression was high at 40.6 percent.[120] Alarmingly, only 3.1 percent had been previously assessed for depression, indicating significant under-recognition and treatment of depression in this patient population.

Research also suggests that there may be differences in the types and rates of treatment for depression in various ethnic groups with diabetes. De Groot et al. evaluated depression treatment patterns in a multicultural sample of patients with diabetes.[121]

African-Americans were found to be less likely to receive treatment for depression. They were also less likely to receive antidepressant treatment, as well as treatment provided by a mental health specialist, when compared to Whites. There were no significant differences in treatment observed between Hispanics and Whites in this study.

Clinical Course

The clinical course of depression in patients with diabetes tends to be chronic and recurrent. In a 5-year follow-up study involving 25 diabetics with an index event of depression, depression recurred in 80 percent of subjects after 1 year and 92 percent of patients after 5 years.[116] During the follow-up period, the average number of episodes of major depression was 4.8, and the average duration of the longest episode of depression during the follow-up period was 16.1 months. Further, in this small longitudinal study, active depression was associated with worsened glycemic control. These findings are consistent with an earlier follow-up study of 37 subjects with depression and diabetes.[122] In that study, 79 percent of patients had a recurrent mood disorder during 5 years of follow-up, and the mean number of mood disorder episodes during the follow-up period was 4.2. The 5-year incidence of depression among diabetic patients without a previous depressive episode was only 10 percent, potentially indicating a significant difference in the risk for recurrence compared to new-onset depression among diabetic patients.

The temporal course and the interrelationship between depression and diabetes are complex and appear to be bidirectional. Research appears to suggest that a prevalent case of either disorder increases the risk for an incident case of the other. Golden and colleagues utilized longitudinal patient data in a study evaluating the directional associations between depression and diabetes.[123] The overall study cohort was separated

into two groups, one with prevalent depression but not diabetes, and one with prevalent diabetes but not depression. Study participants were followed for up to 5 years and the incidence of diabetes and depression were calculated for each group, respectively. Subjects with prevalent depression were found to have a 37 percent increased risk for incident diabetes compared to their non-depressed counterparts. On the other side, subjects with prevalent diabetes receiving treatment had a 52 percent increased risk of incident depression. Interestingly, individuals with untreated diabetes displayed no increase in risk of depression (OR 0.73; CI 0.41-1.30). Likewise, subjects with impaired fasting glucose did not have an increased odds of depression (OR 0.80; CI 0.63-1.02). Potential explanations for this observation may be related to psychological stress associated with complex treatment regimens, or higher level of disease state severity and complications among those who are being treated for diabetes.

The mechanism by which mood and diabetes are related may be biological, psychological, or a combination of both. Depression is associated with a number of biological alterations that may increase the vulnerability of an individual to hyperglycemia and diabetic complications.[124] Increased release of hormones such as cortisol, glucagon, growth hormone, and catecholamines are associated with stress. These hormones act to increase blood levels of glucose, thus potentially altering glycemic control. Immunomodulatory cytokines, such as interleukin-6 and tumor necrosis factor alpha, are expressed in increased levels in diabetic patients and are associated with "sickness behavior," a collection of symptoms with great similarity to the symptoms of depression. Psychosocial factors, such as stress associated with a chronic medical condition, may also result in mood alterations. This is supported by research suggesting that simple awareness of a diagnosis of diabetes is associated with an increased risk of depression when compared to individuals who meet criteria for diabetes but are unaware

of their condition.[125] The destabilizing effect of depression on glycemic control may also be mediated through self-care behaviors and healthy lifestyle activities related to diet and exercise.[126]

Outcomes Associated with Depression in Patients with Diabetes

Depression is associated with increased healthcare utilization, increased healthcare costs, symptom amplification, disability, and increased mortality associated with a variety of other chronic medical conditions.[18,127-132] In patients with diabetes, depressive symptoms are associated with impaired glycemic control, poor treatment adherence, lower functional status, and increased mortality.

Glycemic Control

Depression is associated with hyperglycemia in patients with both T1DM and T2DM.[55] Meta-analysis of data from 24 cross-sectional studies indicates a modest correlation between depression and hyperglycemia (r = 0.17; CI 0.13 - 0.21). This correlation was similar among subjects with both type 1 and type 2 diabetes (r = 0.19; CI 0.12 - 0.25 vs. r = 0.16; CI 0.09 - 0.22). The correlation between depression and hyperglycemia appears to be greater when a structured diagnosis of depression is used, rather than self-rated assessment (r = 0.28; CI 0.20 - 0.36 vs. r = 0.15; CI 0.11 - 0.19). While the absolute value of this correlation is modest at best, in practical terms treatment of depression could result in a 17 percent increase in the proportion of diabetic patients achieving glycemic treatment goals.[55]

The causal directionality of the association between depression and glycemic control in patients diagnosed with diabetes is not clear. Much of the research in this area

has been cross-sectional in nature; the prospective studies that do exist indicate that the relationship is bidirectional - that depression causes hyperglycemia and hyperglycemia exacerbates depression.[133] Some research indicates that the influence of depression on glycemic control is mediated through self-care behaviors. This research suggests that patients with depression are less likely to adhere to self-care behaviors such as diet, exercise, and self monitoring, and this ultimately results in poorer glycemic control.[126]

Diabetic Complications

Diabetes is associated with a number of significant medical complications including nephropathy, retinopathy, neuropathy and an increased risk for heart attack and stroke. A meta-analysis by de Groot et al. evaluated the association between depression and diabetic complications across 27 studies published between 1979 and 1999.[134] While no temporal relationship (i.e., the direction of the causal relationship) could be established, depression was correlated with retinopathy ($r = 0.17$, $p < 0.001$), nephropathy ($r = 0.25$, $p < 0.001$), neuropathy ($r = 0.28$, $p < 0.001$), sexual dysfunction ($r = 0.32$, $p < 0.001$), and macrovascular complications ($r = 0.20$, $p < 0.001$). The overall correlation between depression and all complications combined was significant ($r = 0.25$; $p < 0.001$). In addition to being associated with the presence of a diabetic complication, depression was also associated with an increased number and increased severity of complications. Of note, the strongest correlation between depression and a diabetic complication was seen with sexual dysfunction. It is unclear whether this correlation is due to a destabilizing effect of depression on glycemic control, or whether this correlation is intrinsically related to depression or depression treatment. Notably, sexual dysfunction (especially decreased interest) may be associated with depression in the absence of

treatment.[135] In addition, many antidepressant treatments are associated with sexual dysfunction (especially anorgasmia and/or impotence).[136] Moderate correlations were also seen between depression and nephropathy, neuropathy, and macrovascular complications.

Treatment Adherence

Depression has a well established association with poor treatment adherence across a variety of disease states.[137] A number of studies specifically evaluating the influence of depressive symptomatology on diabetic medication adherence have been performed (See Table 1.18).[138-144] This research suggests that the presence of depression is associated with a small (~5%), but statistically significant reduction in diabetic medication adherence. This small reduction in adherence to diabetic medications is clinically significant in light of the overall poor level of medication adherence exhibited by patients on oral hypoglycemic, and the significant clinical and financial consequences of suboptimal levels of medication adherence in this population.[86,92,94,103,145]

A major limitation is that most of these studies were not designed to evaluate the directional effects between depression and medication adherence. That is to say, they were not designed to evaluate whether depression caused poor diabetic medication adherence, or whether poor diabetic medication adherence resulted in diabetic complications which ultimately led to the development of depression.

Table 1.16 Studies evaluating association between depression and diabetic medication adherence.

Author, year	n	Design	Depression Measure	Adherence Measure	Influence of Depression on Adherence
Ciechanowski, 2000	367	Cross-sectional	HSCL-20	Percentage of days in treatment interruption	High depression symptom severity: 14.9%† Medium depression symptom severity: 9.3% Low depression symptom severity: 7.1%
Lin, 2004	4463	Cross-sectional	PHQ-9	Percentage of days lacking medication	Non-depressed 18.8%‡ Depressed 24.50%
Kilbourne, 2005*	203	Prospective/Retrospective	PHQ-9	EMC: percent of days with correct number of doses; CPR, percent of days with with adequate medication	Depression associated with lower adherence by SR and CPR. EMC and PR adherence were similar amoung depressed and non-depressed patients.
Nau, 2005*	1454	Retrospective	Antidepressant use	Medication possession ratio	Adequate AD treatment assocaited with higher MPR when compared to inadequate AD treatment and no AD treatment.
Kalsekar, 2006	1326	Retrospective	ICD-9 code	Medication possession ratio	Non-depressed 73%†† Depressed 66%
Gonzalez, 2007	879	Cross-sectional	HANDS	Dichotomized response to question about missed medication doses in past 7 days	2.3-fold increase in odds of missing dose of DM medication; Each 1 pt increase in HANDS score associated with 1.12-fold increase in odds of missing
Nau, 2007*	391	Cross-sectional	PHQ-8	SR medication use behaviors	Depression associated with significantly worse medication adherence

n, number of subjects; HMO, health maintenance organization; HSCL-20, Hopkins Symptom Checklist-20; PHQ, Patient Health Questionnaire; CPR, computerized pharmacy records, EMC, electronic monitoring caps; SR, self-report; PR, physician report; MPR, medication possession ratio; HANDS, Harvard National Depression Screening Scale; NI, not indicated

*, results reported herein based on abstract

†, indicates high severity group significantly greater proportion of days in interruption compared to low severity group, p=0.04

‡, statistically different from depressed group after controlling for covariates: age, sex, marital status, education, ethnicity, medical comorbidity, diabetic complications, treatment intensity, and primary care physician

††, statistically different from depressed group with a p <0.001

Morbidity and Disability

Depression is associated with an increased number of diabetic symptoms and symptom amplification in patients with diabetes. The presence of a psychiatric diagnosis (most commonly depression or anxiety) was associated with a nearly 2-fold increase in the number of diabetic symptoms reported by a group of 144 patients with diabetes.[146] In a study involving 407 subjects with diabetes, presence of depression was associated with increased diabetic symptom reporting after controlling for important covariates including comorbidity, diabetic complications, and diabetes type.[147] In a survey of 4168 subjects with diabetes, Ludman et al. found that after controlling for clinical and demographic covariates, an elevated PHQ-9 score was associated with increased reporting of diabetic symptoms when compared to subjects without depressive symptoms.[148] In this study, there was a clear relationship between the number of depressive symptoms and the number of diabetic symptoms, with incrementally increasing PHQ-9 scores closely associated with increased number of diabetic symptoms.

A recent survey conducted by the World Health Organization illustrates the relationship between depression and overall health status for patients with a variety of chronic medical conditions, including diabetes.[18] Based on a survey administered to 254,404 patients from 60 countries worldwide, depression was found to be present in 9.3 percent of respondents with diabetes. Based on composite health status score, comorbid depression and diabetes were associated with greater health impairment than that which would be expected from the individual contributions of each disease state separately, suggesting a synergism between the two diseases in terms of effect on overall health status.

Mortality

Depression is associated with increased mortality in patients with a number of chronic medical conditions, including coronary artery disease, myocardial infarction, and stroke.[127-130] As in these other chronic disease states, depression appears to increase the risk for mortality among patients with diabetes.[149-154] The mortality hazard ratio independently attributable to depression ranges from 1.33 to 1.63, indicating a 33-63 percent increased risk of mortality in diabetic patients who also have depression over diabetes alone. The presence of even relatively low levels of depressive symptomatology (subsyndromal minor depression) is associated with increased risk of mortality in patients with diabetes.[151] Some research suggests that increased risk for mortality among patients with diabetes and comorbid depression may be mediated through diabetic complications; however, a number of studies that controlled for the presence of diabetic complications found that depression is an independent risk factor for mortality in patients with diabetes.[149,151,153,155]

Treatment of Depression in Patients with Diabetes

Non-pharmacological Treatment

One controlled study of psychotherapy for the treatment of depression in the presence of comorbid DM has been reported in the literature.[156] In this study, a 10-week course of Cognitive Behavioral Therapy (CBT) plus diabetes education was compared to diabetes education alone. Cognitive Behavioral Therapy resulted in better response and remission rates at the end of treatment compared to the education only group (response: 66.6% vs. 29.6%, $p < 0.001$; remission: 70.8% vs. 22.2%, $p < 0.001$). Results at a 6-month follow-up assessment were similarly in favor of CBT. In regards to glycemic

control, no statistically significant reduction in HbA1c was seen at the end of 10 weeks of CBT treatment; however, HbA1c levels were decreased by 0.7 percent in the CBT group and increased by 0.9 percent in the control group at the 6-month follow-up ($p = 0.04$). The level of treatment response appeared to have an effect on glycemic control, as remission of depressive symptoms with CBT was associated with significantly lower mean HbA1c at the end of treatment and at the 6-month follow-up. Finally, and somewhat unexpectedly, participation in the CBT group was associated with a decline in self-monitoring of blood glucose levels over time.

Pharmacological Treatment

A number of clinical studies have evaluated the pharmacological treatment of depression in patients with diabetes (See Table 1.19). Studies of the antidepressant medications nortriptyline[157] and bupropion,[158] as well as the SSRIs sertraline,[159] fluoxetine,[160,161] paroxetine,[161] and escitalopram[162] suggest that these medications are effective acute-phase treatments for depression associated with diabetes.

While the clinical literature supports the efficacy of antidepressant medications for the treatment of depression in patients with diabetes, the effect of antidepressant treatment on clinical measures of glycemic control is less clear. No consistent effect of treatment for depression on outcomes associated with diabetes has been demonstrated. In an early study by Lustman et al., path analysis was conducted to evaluate the direct and indirect effects (mediated through improvement in depressive symptoms) of nortriptyline on glycemic control.[157] While nortriptyline treatment improved depressive symptoms, and this improvement was associated with improvement in glycemic control, a direct

hyperglycemic effect of nortriptyline negated the indirect positive effect on glycemic control.

In the only placebo-controlled acute-phase treatment trial involving an SSRI, no significant improvement in glycemic control was observed with fluoxetine treatment.[160] The lack of significant findings regarding improved glycemic control may be related to the short duration of observation in acute-phase depression treatment trials and/or insufficient statistical power. HbA1c reflects the average level of glycemic control over a period of up to 120 days, and therefore, might not reflect changes in glycemic control over the course of a typical 8-12 week acute-phase clinical trial. In addition, these studies tend to be small and underpowered to detect modest changes in glycemic control.

Only one long-term, placebo-controlled, maintenance-phase study involving SSRI treatment of depression in patients with diabetes has been published.[163] This placebo-controlled study evaluated the maintenance efficacy of sertraline over 52 weeks following acute response. As expected, sertraline maintenance treatment was effective for preventing depression recurrence after acute response was achieved. In the 16-week acute phase open-label portion of the study, glycemic control improved (mean change in HbA1c -0.4% +/- 1.5%, p=0.002); however, no further improvement in glycemic control was seen during the maintenance phase, and the improvements in glycemic control seen during the acute phase persisted equally in both the active and placebo maintenance groups. No post-recurrence HbA1c values were obtained in order to evaluate the potential consequences of depressive recurrence on glycemic control in this study.

Table 1.17 Studies of antidepressant treatment for depression in patients with diabetes

Author, year	Treatment phase	Intervention	n	Duration	Depression outcomes	Diabetes outcomes
Goodnick, 1997	Acute	open-label SER, 50 mg/day	28	10 weeks	Improvement in HAMD (22.6 ±3.4 to 4.9 ±5.9, p<0.001) and BDI (21.9 ±10.5 to 12.7 ±8.3, p<0.001)	Improved dietary compliance, reduction in HbA1C in 76% of subjects with baseline HbA1C >8.0 (p=0.018)
Lustman, 1997	Acute	NOR, level: 50-150 ng/mL Placebo	14 14	8 weeks	Favored NOR (ΔBDI: -10.2 vs. -5.8, p=0.03)	Path analysis indicates that NOR associated with worsened HbA1C
Lustman, 2000	Acute	FLU, up to 40 mg/day Placebo	27 27	8 weeks	Favored FLU (ΔBDI: -14.0 vs. -8.8, p<0.03; ΔHAMD: -10.7 vs. -5.2, p=0.01)	No difference in ΔHbA1C
Gulseren, 2005	Acute	FLU, 20 mg/day PAR, 20 mg/day	11 9	12 weeks	FLU and PAR associated with within-group reductions in HAMD, no difference in between-groups ΔHAMD.	No difference within- or between-groups in ΔHbA1C
Amsterdam, 2006	Acute	open-label ESC, 10-20 mg/day	14	16 weeks	ESC associated with significant improvements in HAMD, CGI-S and CGI-I	No effect on HbA1C or FBG
Lustman, 2006	Maintenance	SER, mean dose=117.9 mg/day Placebo	79 73	52 weeks	SER associated with longer time to relapse of depression (>365 days vs. 251 days, p=0.02)	Reduction in HbA1C seen during open-label acute-phase of trial, however no additional reduction during maintenance treatment.

n, number of sujects; DM, diabetes mellitus; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; NOR, nortryptiline; CBT, cognitive behavioral therapy; BGM, blood glucose monitoring; FLU, fluoxetine; PAR, paroxetine; ESC, escitalopram; SER, sertraline; CGI-S, clinical global impression-severity; CGI-I, clinical global impression-improvement

In an open-label study of the atypical antidepressant bupropion, remission of depression was observed for 87.3 percent of subjects during acute-phase treatment (10 weeks).[158] Of those who remitted during acute-phase treatment, 100 percent who completed the maintenance-phase (24 weeks) remained depression-free. Remission of depressive symptoms was associated with a 0.6 percent (± 1.1%) reduction in HbA1c ($p<0.001$), compared to a 0.1 percent (± 1.3%) reduction in patients who did not achieve remission ($p=0.7$) in the acute-phase of the study. As in the sertraline maintenance study, improvements in glycemic control during the acute-phase persisted throughout the depression-free maintenance period. Further, regression analyses indicate that improvement in depressive symptoms had a significant and independent effect on reducing HbA1c after controlling for baseline HbA1c and changes in self-care behaviors, monitoring, and body mass index during the course of the study. No subjects in this study who entered the maintenance phase experienced a recurrence of depressive symptoms, making it impossible to determine the nature of any association between recurrence of depressive symptoms and glycemic control.

Effect of Treatment on Diabetic Medication Adherence

Katon et al. evaluated the influence of antidepressant adherence on medication adherence in a number of chronic disease states, including diabetes.[164] Adherence with antidepressant treatment was defined as: a) Medication Possession Ratio (MPR) ≥ 80 percent; and b) No evidence of a medication gap ≥ 15 days during the first 90 days of antidepressant treatment. Diabetic medication adherence was evaluated by MPR, with an MPR ≥ 80 percent being identified as adherent. Logistic regression analysis, including age, sex, insurance plan type, psychiatric services, anxiety or depression diagnosis, pre-

index medication adherence, and antidepressant dosing as covariates, was used to evaluate the effect of antidepressant adherence on diabetic medication adherence.

Katon and colleagues analyzed pharmacy prescription data for 8,040 patients, 2,518 of whom were receiving treatment for diabetes. In the 6-month period prior to initiation of antidepressant medication, 77 percent of subjects with diabetes were adherent to their diabetic medication regimen. In the year after initiation of antidepressant medication, diabetic medication adherence dropped to 64.4 percent. During the period of concomitant treatment, antidepressant medication adherence was lower than diabetic medication adherence (36.3% vs. 64.4%). After controlling for the covariates mentioned previously, adherence to antidepressant treatment was associated with a 1.82-fold increase in the odds of adherence to diabetic medications. Notably, the influence of depression symptom severity was not accounted for in this study. It is unclear whether the association between antidepressant treatment and diabetic medication adherence was related to patient-specific medication-taking behaviors, or whether the association was mediated through reduction or resolution of depressive symptoms with antidepressant treatment.

Collaborative Care Programs

Multi-disciplinary collaborative care has gained increasing attention as a possible intervention to improve clinical outcomes associated with a range of medical and psychiatric conditions. The outcomes associated with a collaborative care program consisting of nurse-administered education and support of depression treatment for patients with depression and diabetes was reported by Katon and colleagues.[165] When compared to treatment as usual, enhanced care was associated with greater improvements

in adequacy of antidepressant treatment, antidepressant medication adherence, and depressive symptoms. Although enhanced care was associated with better depression treatment outcomes, no effect on diabetes self-care activities or glycemic control over 12 months was seen.[166] In addition, enhanced care had no significant effect on antihypertensive and lipid-lowering medication adherence. Interestingly, hypoglycemic medication adherence was actually lower in the intervention group compared to controls, perhaps suggesting that patients were overburdened by the enhanced care intervention. Notably, enhanced care in this study was focused on support and guidance for treatment of depression, and no diabetes-specific interventions were conducted.

These results are similar to those found during a subgroup analysis of another collaborative care intervention in older patients with depression.[167] Collaborative depression care in this study resulted in improvements in depression outcomes, but diabetes self-care behaviors (with the exception of weekly exercise days) and glycemic control were unaffected. Similar discouraging results have been found in studies evaluating psychoeducational interventions for patients with diabetes and subsyndromal depression, as well as collaborative care programs among a cohort of predominantly Hispanic patients with diabetes and depression.[168,169]

It is not clear why these enhanced depression care programs have failed to demonstrate significant effects on diabetes care behaviors, diabetes medication adherence, and glycemic control. It has been suggested that concurrent intensive depression and diabetes treatment regimens might overwhelm these patients, and self-care activities such as glucose monitoring, exercise, and medication adherence might suffer as a result.

Antidepressant Exposure and Risk of New-onset Diabetes

A number of recent studies have evaluated antidepressant medication exposure and its association with diabetes. Brown et al. evaluated the relationship between antidepressant medication exposure and new-onset diabetes over a 10-year period.[170] SSRI monotherapy was associated with lower risk of observing new-onset diabetes compared to TCA monotherapy (OR 0.76, 95% CI 0.63 – 0.91); however, an increased risk of new-onset diabetes diagnosis was observed for individuals taking SSRI/TCA combination therapy compared to individuals receiving TCA monotherapy (OR, 1.88, 95% CI 1.37 – 2.59). There was no association observed between use of other combinations of antidepressant medication and risk of diabetes, compared to patients receiving TCAs only.

Rubin et al. evaluated antidepressant medication exposure as a risk factor for developing diabetes among a group of subjects at high risk for developing diabetes.[171] Baseline antidepressant use was associated with a 3.48-fold increased in the odds of diagnosis of diabetes over a mean follow-up period of 3.2 years. Intermittent antidepressant exposure was not associated with a statistically significant increase in odds of diabetes diagnosis, while continuous antidepressant use was associated with a 2.6-fold increase in risk. These data suggest that increased levels of antidepressant medication exposure may be associated with increased risk for development of diabetes.

Research conducted by Andersohn et al. would likewise suggest that the extent of antidepressant exposure is a key factor in risk of diabetes associated with antidepressant exposure.[172] Like Rubin, Andersohn found that higher levels of exposure to antidepressant treatment (in this case, $\geq$ 24 months of moderate to high dose treatment) were associated with increased risk of diabetes, but not shorter periods or lower dosages. Of note, Brown, Rubin, and Andersohn evaluated new-onset diabetes and did not

evaluate the association between antidepressant exposure and glycemic control among diabetic patients.

A case-control study conducted by Derijks et al. reiterates the role that duration of medication exposure may play in the relationship between antidepressant exposure and diabetes.[173] Derijks and colleagues found that antidepressant exposure was associated with spontaneous adverse event reporting of diabetes and other forms of hyperglycemia (OR 1.52, 95% CI 1.20 – 1.93). In addition, longer term antidepressant use (> 1 year) was associated with hyperglycemia, while short-term treatment (0 - 1 year) was not.

The association between antidepressant use and new-onset diabetes may be associated with metabolic side effects associated with antidepressant treatment. Raeder et al. found that SSRI use was associated with obesity and hypercholesterolemia.[174] Subgroup analyses revealed that the association was heterogeneous among the specific SSRI agents. Paroxetine, but not citalopram, was associated with obesity. Sertraline, fluoxetine, and fluvoxamine (analyzed as a single group) were associated with obesity and hypercholesterolemia. Citalopram appeared to have the most favorable metabolic profile among the agents evaluated.

Some antidepressant medications may be associated with a more direct deleterious effect on glycemic control. Imipramine, but not fluoxetine, was associated with an increase in fasting blood glucose levels in an evaluation of the relationship between short-term antidepressant use (8 weeks) and glycemic control.[175] A number of animal studies suggest the possibility of a direct hyperglycemic effect for a variety of antidepressant medications; however, these findings have not been consistently replicated in human subjects.[176,177] As discussed previously, treatment of depression with antidepressant medications has been associated with improved glycemic control in some

studies, but in those studies improvement in glycemic control was evaluated in relationship to treatment response, rather than simple medication exposure.

Summary

Diabetes and depression are individually significant public healthcare problems in the United States. The combination of the two is common, and the presence of a diagnosis of diabetes has been associated with a 2-fold increase in the odds of an individual being diagnosed with depression or experiencing significant depressive symptoms. Comorbid depression is associated with worsened outcomes associated with diabetes, including hyperglycemia, lower rates of medication adherence, and increased risk of diabetic complications and death. Some research suggests that antidepressant exposure may be associated with new-onset diabetes. While a number of effective treatments for depression in this population exist, research has yet to demonstrate that treatment and resolution of depression in this patient population has a significant influence on glycemic control, diabetes treatment adherence, and complications associated with depression.

MEDICATION ADHERENCE AND PERSISTENCE

Optimal medication-taking is essential to achieving the intended therapeutic outcome. Medication-taking behaviors have been shown to be important factors associated with clinical and economic outcomes for a wide variety of medical conditions including hypertension, human immunodeficiency virus infection, hepatitis C, schizophrenia, as well as diabetes and depression, as previously discussed.[178-184] The purpose of this section is to discuss terminology and definitions for the constructs related to medication-taking behavior that will be evaluated in this study.

Pharmacy Claims Data

Medication-taking behavior can been evaluated in a number of ways including patient self-report, clinician assessment, pharmacy refill records, electronic monitoring, and serum blood levels. This study utilized pharmacy refill records to evaluate medication-taking behaviors in patients with diabetes and depression. The primary benefit to using pharmacy claims data for evaluations of medication adherence and persistence in large populations is the relative efficiency compared to other methods.[185] Prescription claims data may also provide longitudinal data on medication refill patterns that might otherwise not be available.

The use of pharmacy claims data to evaluate medication adherence has been validated against other measures of medication adherence such as patient self-report, pill count, and biological measures of drug consumption.[186] The use of prescription claims data as a proxy for medication adherence is predicated on the assumption that obtaining a medication from the pharmacy is a valid marker for medication consumption. While this

might not always be the case, research suggests that medication acquisition is associated with drug consumption as measured by drug levels and physiological effect.[186]

For pharmacy claims data to be a valid marker for medication adherence, it is necessary that the dataset contain complete medication data for an individual subject. If an individual has multiple sources of medications, such as multiple third-party prescription plans or physician samples in addition to pharmacy-dispensed medications, pharmacy claims data may be an inaccurate reflection of medication acquisition and availability. In addition, if a patient pays out-of-pocket for some of their medications, those data may not be captured in secondary pharmacy claims datasets. With those limitations in mind, if the data are complete and there is a low likelihood of subjects obtaining medications from sources not captured in the database, pharmacy claims data can be useful for identifying non-adherence with high specificity.[185]

Defining and Operationalizing Medication-taking Behaviors

Two constructs can been used to describe medication-taking behavior: medication adherence (synonym: compliance), and medication persistence. The following sections discuss issues related to medication adherence and persistence, with a particular focus on medication possession ratio as a measure of adherence, and evaluation of medication persistence.

Medication Adherence

Medication adherence is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[187] Medication adherence is measured in terms of a time period and should be reported as a

percentage.[188] In studies utilizing pharmacy claims records to evaluate medication adherence, adherence is commonly operationalized by the medication possession ratio (MPR). The MPR is calculated using the days' supply information from pharmacy claims data.

The MPR is essentially the ratio of the sum of the days of medication supplied divided by the number of days of observation.[185,188,189] A number of variations in methodology have been used to calculate the MPR, with variability in the methodology being related primarily to calculation of the denominator. The denominator of the MPR has been determined using a fixed time interval, or alternatively, by using a variable time period based on refill intervals. In a review of 136 studies utilizing medication adherence measures, the MPR was reported in 57 percent (n=77) of published articles.[185] Among these studies, the majority (55%, n = 42) utilized a fixed interval to calculate the denominator for the MPR calculation. Thirty nine percent (n = 30) used a denominator calculated on the basis of refill intervals. Hess et al. compared a variety of adherence measures including a fixed-interval MPR and an MPR calculation based on the refill interval (in this case, termed the MPRm).[189] The fixed interval MPR returned adherence estimates that were similar to a number of other prescription claims-based adherence measures (e.g. Continuous measure of medication acquisition, proportion of days covered), while the MPRm returned a higher estimate of adherence. In addition the MPRm was found to be particularly sensitive to attrition and instances when only a single prescription refill is obtained.

A formal taxonomy of methods for assessing medication adherence with pharmacy refill data has been described by Steiner and Prochazka.[186] According to their taxonomy, methods of calculating medication adherence can be characterized on the basis of three attributes: the nature of the adherence variable (Continuous or Dichotomous); the

number of refill intervals in the observation period (Single or Multiple); and, whether the variable measures the presence or absence of access to medication (Available or Gap). Using this taxonomy, medication adherence measures can be notated by using a single letter to describe the variable on each of the three attributes. For example, a CMA measure of medication adherence would be a continuous variable evaluating medication availability over multiple refill intervals. The MPR is, therefore, a CMA measure of medication adherence when it is calculated based on pharmacy claims data over an observation period covering multiple refill intervals.

In addition to being treated as a continuous measure of adherence, the MPR value may also be dichotomized (i.e., compliant vs. non-compliant), based on comparison of an individual subject's MPR with a threshold MPR. A commonly used MPR threshold for dichotomizing medication adherence data is 0.80 (i.e., MPR $\geq$ 0.80 = compliant; MPR < 0.80 = non-compliant). This value of an MPR threshold has been used in a number of studies in a variety of chronic disease states such as diabetes and hypertension,[94,96,98,100] while studies in other disease states (e.g., HIV infection, hepatitis c infection) have used higher MPR thresholds to operationally define dichotomized medication adherence.[179,180]

Medication Persistence

ISPOR defines medication persistence as: "the duration of time from initiation to discontinuation of therapy".[187] Medication persistence is essentially a measure of the length of time that an individual stays on an initial treatment. A common method of evaluating medication persistence with pharmacy claims data involves calculation of a "permissible gap".[187] A subject's pattern of prescription refills are followed longitudinally until the length of time between prescription refills exceeds the

predetermined permissible gap.[190] A common timeframe used for the permissible gap is 1.5 times the days' supply of preceding prescription, although a variety of multiples ranging from 1.5 to 3.0 have been used.[190,191] Alternatively, fixed-intervals ranging from 15 to 120 days have been used to identify non-persistence.[190-193] Medication persistence is measured as a continuous variable in terms of whole days. A strength of this method of evaluating medication persistence is that it lends itself to methods of survival analysis, such as Kaplan-Meier analysis and Cox survival regression analysis.[188,191] This continuous measure can also be dichotomized into persistent and non-persistent, indicating a person's persistence status at a given point in time (e.g., 3- or 12-month persistence).

STUDY RATIONALE

The overall objective of this research is to evaluate the relationship between diabetes and depression, with a specific focus on antidepressant medication-taking patterns in patients with diabetes. First, this study will seek to evaluate diabetes as a risk factor for the development of new-onset depression among a cohort of indigent care patients. Risk factors for incident cases of depression among patients with prevalent diabetes will also be identified. In addition to factors related to the diagnosis of depression, the pharmacoepidemiology of antidepressant use in patients with comorbid depression and diabetes will be evaluated. This study will provide insight into antidepressant medication utilization patterns among patients with diabetes and depression, the relationship between a diagnosis of diabetes and antidepressant medication adherence, and the relationship between antidepressant treatment adherence and glycemic outcomes in patients with diabetes.

These areas as outlined represent understudied topics in the health services and medical outcomes literature. It is hoped that by addressing these research topics, the results of the current study will aid healthcare providers in helping to inform their provision of medical care for patients with co-occurring diabetes and depression.

OBJECTIVES AND HYPOTHESES

The objectives and related hypotheses of this study are presented in the following section.

Objective 1

Objective 1 is to evaluate diabetes as a risk factor for depression in a population of indigent primary care patients.

H_0 1.1: There is no statistically significant association between diabetes diagnostic status and incident depression diagnostic status among indigent primary care patients.

H_0 1.2: After controlling for age, gender, ethnicity, marital status, and Charlson score there is no statistically significant association between diabetes diagnostic status and incident depression diagnostic status among indigent primary care patients.

Objective 2

Objective 2 is to evaluate risk factors for an incident diagnosis of depression among patients with diabetes.

H_0 2.1: After controlling for the influence of covariates, there is no statistically significant association between **age** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 *2.2:* After controlling for the influence of covariates, there is no statistically significant association between **gender** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 *2.3:* After controlling for the influence of covariates, there is no statistically significant association between **race/ethnicity** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 *2.4:* After controlling for the influence of covariates, there is no statistically significant association between **marital status** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 *2.5:* After controlling for the influence of covariates, there is no statistically significant association between baseline **HbA1c level** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 *2.6:* After controlling for the influence of covariates, there is no statistically significant association between **number of diabetic complications** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 *2.7:* After controlling for the influence of covariates, there is no statistically significant association between the **Charlson score** and depression diagnostic status in patients with a diagnosis of diabetes.

Objective 3

Objective 3 is to evaluate the association between diabetes diagnostic status and antidepressant medication utilization patterns.

H_0 3.1: There is no statistically significant relationship between diabetes diagnostic status and **class of initial antidepressant** (i.e., SSRI, non-SSRI) prescribed for patients with depression.

H_0 3.2: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant switch status** in patients with depression.

H_0 3.3: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant discontinuation status** in patients with depression.

H_0 3.4: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant 6-month MPR**.

H_0 3.5: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant 12-month MPR**.

H_0 3.6: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **time to antidepressant non-persistence status**.

H_0 3.7: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **3-month antidepressant persistence status**.

H_0 3.8: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **12-month antidepressant persistence status**.

Objective 4

Objective 4 is to evaluate the association between class of initial antidepressant medication treatment and antidepressant medication-taking behaviors in patients with diabetes.

H_0 4.1: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **antidepressant switch status** after controlling for appropriate covariates.

H_0 4.2: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **antidepressant discontinuation status** after controlling for appropriate covariates.

H_0 4.3: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **6-month antidepressant MPR** after controlling for appropriate covariates.

H_0 4.4: Among subjects with diabetes, there is no statistically significant between type of initial antidepressant medication treatment and **12-month antidepressant MPR** after controlling for appropriate covariates.

H_0 4.5: Among subjects with diabetes, there is no statistically significant between type of initial antidepressant medication treatment and **time to antidepressant non-persistence status** after controlling for appropriate covariates.

H_0 4.6: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **3-month antidepressant persistence status** after controlling for appropriate covariates.

H_0 4.7: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **12-month antidepressant persistence status** after controlling for appropriate covariates.

Objective 5

Objective 5 is to evaluate the relationship between antidepressant medication adherence and glycemic control (measured by HbA1c) in patients with diabetes and comorbid depression.

H_0 5.1: After controlling for appropriate covariates, there is no statistically significant relationship between **6-month antidepressant medication MPR** and HbA1c during follow-up.

H_0 5.2: After controlling for appropriate covariates, there is no statistically significant relationship between **12-month antidepressant medication MPR** and HbA1c during follow-up.

Chapter 2: Methodology

CHAPTER OVERVIEW

The purpose of this chapter is to describe the design and methods of this research including institutional review board approval, study design, description of the data sources, study population, study variables, and statistical analyses.

INSTITUTIONAL REVIEW BOARD APPROVAL

This study was approved by The University of Texas at Austin Institutional Review Board (IRB) (study identification number: 2008-06-0007). The study met the requirements for expedited review and was initially approved on 06/17/2008. We requested and received waivers of informed consent and HIPAA authorization from the IRB. These waivers were authorized on the basis that all data collected and analyzed for this study were pre-existing and were already maintained as a part of the participants' existing medical records. In addition, waiver of HIPAA authorization was granted because: 1) there will be minimal risk to the patients; 2) contacting and obtaining HIPAA consent from subjects would be impractical; and 3) obtaining HIPAA consent from patients no longer treated in the CommUnityCare clinic network (formerly Austin Travis County Community Healthcare Clinics) would be impossible.

STUDY DESIGN

This study is a retrospective database study. Patient-level data was extracted from a variety of administrative and clinical databases for individuals who met study inclusion criteria. Demographic information, such as age, gender, ethnicity, and marital status, as

well as clinical information, including diagnosis codes, laboratory results, and prescription records, were utilized as available.

DATA SOURCES

This study utilized data obtained from a number of administrative and clinical data sources. These data sources and the related data elements are summarized in Appendix C. Data for this study consisted of administrative and clinical data obtained during the course of usual care in a community indigent care network. The primary source of data for this project is the NextGen Healthcare Information System (NHIS). Prescription claims data and laboratory data were obtained from pharmacy and laboratory datasets and linked to the primary data source. A brief description of each of the data sources follows.

Administrative and Clinical Data

The NHIS system is the practice management and electronic health record system utilized by CommUnityCare, a nonprofit organization providing healthcare services for indigent patients in Austin and Travis County, TX. The NHIS system contains information related to practice management (appointments, billing information, etc.), as well as clinical documentation and charting for service encounters occurring within the clinic system. There are two primary subsystems within the NHIS as implemented by the clinics, the Enterprise Practice Management system (EPM) and the Electronic Medical Record system (EMR).

The EPM is the administrative management system used to schedule patient appointments and to facilitate billing. The EMR is the clinical management system used

in community healthcare centers and contains patient-level medical data. Data elements available through NHIS which will be used for this study include demographic information, service eligibility data, medical encounter data and clinical laboratory data.

Pharmacy Data

Prescription claims data were collected from two sources. During the period of time covered by this study, the clinic network operated onsite class A pharmacies located within some of the community health clinics. Pharmacy services are also provided by a chain community pharmacy. Patients receive their prescriptions at a reduced rate if they obtain them through the onsite or participating community pharmacies. These pharmacy data sources were utilized to obtain prescription claim records for study subjects.

Data elements associated with pharmacy claims include: a unique and de-identified study identification number, prescriber name, dispense date, date the prescription was written, national drug code, dispensed quantity, prescription quantity, and days supply of medication. These data elements were used as described in subsequent sections to facilitate evaluation of medication-taking behaviors.

Laboratory Data

Laboratory services are provided for the community health centers by the Laboratory Corporation of America (also known as LabCorp). Data elements included in the laboratory table include: study identification number, type of test, date of test, laboratory test result, result description, result units, and ordering provider. Laboratory data were extracted from the EMR with supplementary data obtained, as necessary, from archived laboratory data maintained in a separate LabCorp data table. These

supplementary data were identified and incorporated into the final database by clinic information technology personnel at the request of the researcher.

STUDY POPULATION

Data were extracted only for adults receiving medical care within the CommUnityCare clinic network. This study utilized data for both male and female patients, as well as patients of all ethnicities. No data was systematically excluded from the data extraction on the basis of any demographic or clinical factors, other than those detailed in the inclusion and exclusion criteria.

Inclusion Criteria

Data were initially extracted for individuals meeting the following criteria:

1) Subject has one or more medical encounter(s) in one of the CommUnityCare clinics between October 1, 2004 and September 30, 2008; and,
2) Age between 18 and 64 years.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the data extraction:

1) Medicare benefits coverage;
2) Medicaid benefits coverage; or
3) Clinic eligibility determination as homeless.

Rationale for Inclusion and Exclusion Criteria

The inclusion and exclusion criteria implemented for this study are based on a number of practical and methodological considerations. The preliminary case identification screen was conducted by clinic personnel based on the study inclusion and exclusion criteria. Subjects with Medicare or Medicaid coverage were excluded due to the lack of available prescription claims data within the clinic health information infrastructure for these individuals. Homeless subjects were excluded from this study due to the way in which the clinic assigns service eligibility to these clients. Service eligibility for these clients is intermittent and assigned in short-term increments.

TIME FRAME

This study utilized data collected during clinic visits occurring between October 1, 2004 and September 30, 2008. This study period was chosen based on a number of factors including the implementation status of the NHIS in the clinics, data availability, and study requirements.

DATA MANAGEMENT

This study utilized administrative and clinical data obtained from multiple data sources. The NHIS is considered the primary data resource for this research. Data were managed using Microsoft Office Access 2007. Microsoft Office Excel 2007 was used as a secondary data management system in order to perform certain calculations or data manipulations, as necessary. All statistical modeling and analyses were conducted using PASW version 18.0.

STUDY VARIABLES

The purpose of this section is to provide the operational definition for each of the dependent and independent study variables. The operational definitions for each of the variables of interest, as well as covariates included in the analyses are described in the following section. The study variables, variable coding, variable type, and source are summarized in Appendix D.

Primary Variables of Interest

Diagnosis of Depression

A diagnosis of depression was identified using diagnostic information obtained from computerized medical records. Depression was identified on the basis of International Statistical Classification of Diseases and Related Health Problems, 9th revision clinical modification (ICD-9 CM) diagnostic codes 296.2x, 296.3x, or 311.xx. The presence of a diagnosis of depression was coded as 1 in the analytic dataset, while the absence of a diagnosis of depression was coded as 0. In the final dataset, separate indicator variables were used to identify the presence of depression during the screening period (if applicable) and the follow-up period, based on the analytic strategy detailed later in this chapter.

Diagnosis of Diabetes Mellitus

The presence of a diagnosis of diabetes was determined based on clinical diagnostic data. ICD-9 CM diagnostic code 250.xx was used to identify the presence of a diagnosis of diabetes. The presence of a diagnosis of diabetes was coded as 1 in the analytic dataset, while the absence of a diagnosis of diabetes was coded as 0. As with

depression indicator coding, in the final dataset separate indicator variables were used to identify the presence of diabetes during the screening period and the follow-up period, based on the analytic strategy detailed later in this chapter.

Medication Adherence and Persistence

Medication Adherence

Medication adherence was evaluated as a continuous measure of medication adherence using the medication possession ratio (MPR). The MPR was used as a CMA (continuous, multiple period, medication available) method of measuring medication adherence, according to the taxonomy proposed by Steiner and Prochazka.[186] The MPR is defined as the sum of the number of days of medication supplied during a time interval divided by the number of days during the interval.[188] In the current study, the MPR was calculated for the index antidepressant medication using a fixed observation time frame for the observation interval. Observation time frames of 6 and 12 months were used, depending on the specific hypothesis being tested. Calculations of MPR resulting in values greater than 1.00 for individual subjects were truncated at 1.00 prior to analysis.

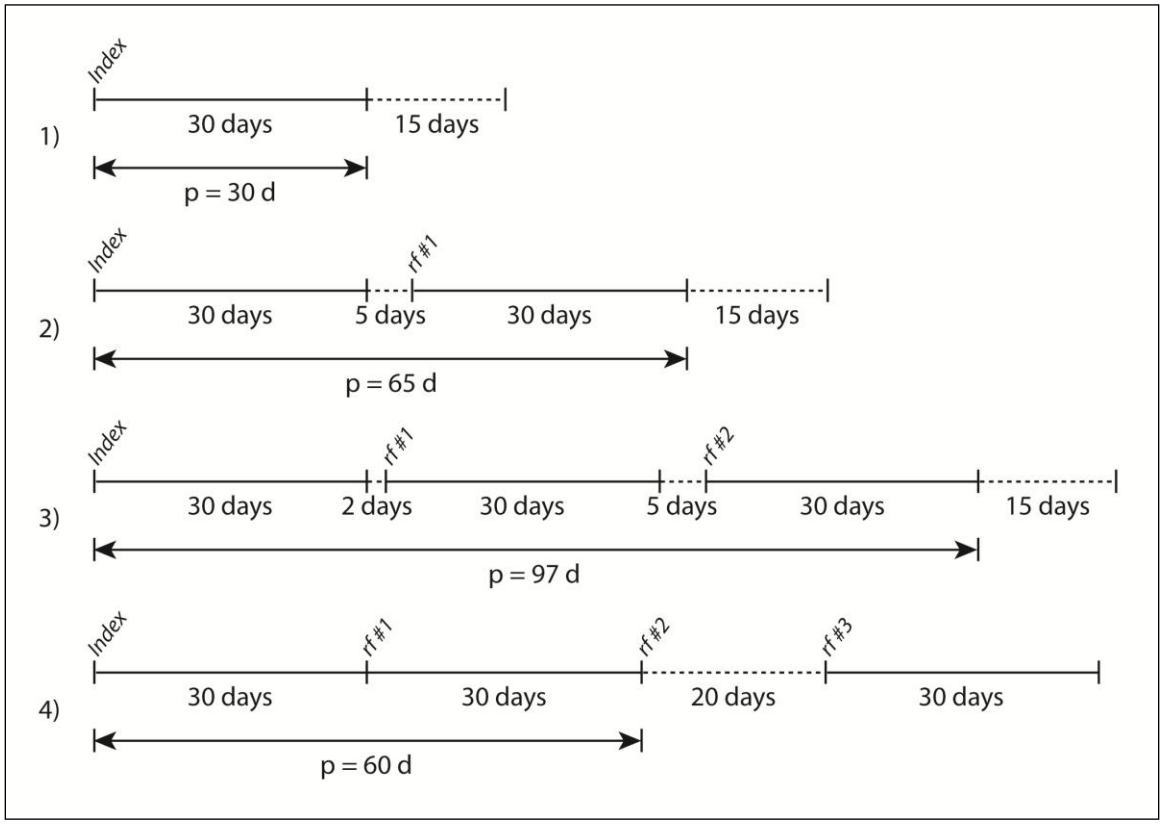
Medication Persistence

Medication-taking behavior was also measured as a function of persistence, or the length of time that the subject remains on continuous therapy once treatment is initiated. Medication persistence is an important component of medication adherence that attempts to capture continuity of medication exposure, a factor that is not captured in the MPR.[188] This is done by evaluating the temporal gaps between medication refills. Persistence was evaluated in terms of both continuous and dichotomous measures. Time to non-

persistence was the continuous measure of persistence, and was measured in days. Persistence in this study was evaluated according to the "permissible gap" method described by Sikka and colleagues.[190] This methodology identifies subjects as non-persistent when a predetermined length of time between the end of the last supply of medication and the time of refilling the subsequent prescription is exceeded. For the purposes of this study, the predetermined period of "permissible gap" time allowed between refills was 15 days.

When an individual subject displayed a gap in medication availability of greater than 15 days, the date of expiration of the days supply associated with the previous prescription fill was considered the conversion to non-persistence, and the period of time between the initiation of the index prescription and this conversion date was calculated in days (Figure 2.1). Continuous time to non-persistence data were used to create dichotomous variables indicating persistence status at 3 and 12 months. Subjects who displayed a total number of persistent days greater than or equal to 90 days were coded as being persistent at 3 months. If the total number of persistent days was equal to or greater than 365 days, patients were coded as being persistent at 12 months.

Figure 2.1 Examples of medication persistence calculation based on four prescription fill patterns.



Solid line indicates days supply period associated with prescription fill; dashed line indicates time period during which days supply from previous fill has expired (i.e. gap); index, index prescription claim; rf, refill; p, persistence time calculated in days

Antidepressant Medication Class

Pharmacy prescription claims data were utilized to evaluate the frequency of type of initial antidepressant medication prescribed for individuals receiving treatment for depression. The original intent was to categorize antidepressant medications according to their pharmacological classification as either a serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or an atypical antidepressant. However, based on preliminary analysis of the available data, the initial antidepressant medication was coded as a dichotomous variable; SSRI antidepressant medications were coded as 0 and SNRI or atypical antidepressant medications were coded as 1. Based on preliminary evaluation of medication utilization patterns observed with tricyclic antidepressant medications, prescription claims for tricyclic antidepressant medications were not included in any of the study analyses. Prescription claims for tricyclic antidepressant medications were generally indicative of low-dose use for indications other than depression.

Antidepressant Discontinuation and Switch

Pharmacy prescription claims data were utilized to evaluate medication utilization patterns. Specifically, this study evaluated rates of antidepressant discontinuation and switch among patients with depression. Discontinuation and switch rates for subjects with diabetes were compared to the rates of discontinuation and switch for subjects without diabetes. Analysis of discontinuation and switch rates by initial class of antidepressant treatment were also conducted.

Antidepressant discontinuation was operationalized as the absence of a pharmacy claim for an antidepressant medication for a continuous period of 60 days following the

expiration of the days supply associated with the previous antidepressant prescription claim. Individuals who were identified as discontinuing antidepressant medication treatment according to this definition were coded as 1 in the analytic dataset, while subjects who did not meet this definition of discontinuation were coded as 0. Discontinuation is distinct from medication non-persistence (discussed earlier), in that discontinuation is indicative of a long-term cessation of medication treatment, whereas non-persistence is indicative of intermittent, short-term cessation of medication treatment that may or may not be followed by a resumption of the index treatment.

Antidepressant switch was operationalized as the absence of a subsequent claim for the index antidepressant medication for a continuous period of 60 days after the expiration of medication supply, during which period of time a claim for an alternative antidepressant medication was observed. Individuals who met this definition of antidepressant switch were coded as 1 in the analytic dataset, while individuals who did not meet this definition were coded as 0. This definition of antidepressant switch attempts to capture individuals who initiate treatment on an antidepressant medication, discontinue their initial treatment for any reason, and switch to an alternate treatment without a substantial lapse in treatment indicative of treatment discontinuation.

Glycemic Control

Glycemic control was evaluated by inspection of HbA1c values at time points described in the analysis section of this chapter, and as available from the laboratory dataset. HbA1c is reported as a percentage and is treated as a continuous variable in analyses related to Objective 5.

Covariates

A number of covariates were included in statistical analyses to control for potential confounding due to various demographic, medication, and clinical factors. Descriptions and operational definitions of the variables which were used as covariates in the various regression models and have not previously been described are presented in the following section.

Demographic Variables

Age

Age was incorporated as a continuous variable, and was obtained from the NHIS. For analyses under Objective 1 and Objective 2, the reference age was the age in years at the start date for the screening period. For all other objectives, the reference age was the age in years at the time of the index antidepressant prescription fill.

Gender

Gender was incorporated as a dichotomous categorical variable and was obtained from the NHIS. For the purposes of all analyses, gender was coded as: female = 0; male = 1. On the basis of this coding, female gender served as the reference comparator group for all regression analyses.

Race/ethnicity

Race/ethnicity was entered into the regression models as a categorical variable. Due to the low frequency of some reported race/ethnicity categories, the following race/ethnicity categories were collapsed to a single "other or unknown" category: Asian,

American Indian/Alaskan, Native Hawaiian, Other Pacific Islander-Not Hawaiian, unreported, and unknown. Therefore, the classification and coding of the race/ethnicity variable was as follows: White-Hispanic = 0; White-non-Hispanic = 1; African-American = 2; other or unknown = 3. While the general convention for incorporating race/ethnicity into statistical modeling is to use dummy coding such that the comparator group is White non-Hispanic, due to the fact that the overwhelming majority of subjects included in this study were classified as White Hispanic, this group was used as the comparator for all other ethnic classifications.

Due to modeling considerations for analyses related to Objective 4, and after preliminary inspection of the frequency distribution of the race/ethnicity variable for subjects included in these analyses, the race/ethnicity classification for these models were further collapsed to two groups: White Hispanic = 0; and non-White Hispanic = 1. This allowed for removal of two variables from the Objective 4 statistical models, increasing the stability of the regression solution.

Marital Status

Marital status was incorporated into the regression models as a categorical variable. Due to the low frequency of some reported marital status categories, the following marital status categories were collapsed to a single category labeled "Other or unknown": divorced, widowed, legally separated, and unknown. The coding of the marital status variable is as follows: single = 0; married = 1; divorced, widowed, other or unknown = 2. On the basis of this coding, marital status of single was the reference comparator group in the regression models for all other marital status classifications.

Clinical Variables

Comorbidity Index

The Charlson comorbidity index (CCI) was developed to predict risk of 1-year mortality attributable to medical comorbidity.[194] Romano and colleagues adapted the CCI for use with ICD-9 CM diagnostic codes.[195] The Charlson score has been used in a variety of epidemiological studies as a continuous marker of comorbidity.[196-198] The Romano implementation of the CCI was used to adjust for comorbidity via inclusion as the Charlson score in the statistical tests. The Charlson score was treated as a continuous variable for the purposes of this study. ICD-9 CM codes were converted to Charlson scores based on the classifications proposed by Romano. These classifications are presented in Appendix E.

Diabetic Complications

The presence of diabetic complications (e.g., retinopathy, nephropathy, etc.) was determined based on ICD-9 CM diagnostic codes. The presence of individual complications was coded in the analytic dataset according to the ICD-9 CM diagnostic codes presented in Appendix F. A separate indicator variable was coded 0 or 1 based on the presence of a diagnostic code for the specific complication. Individual indicator variables were constructed for retinopathy, nephropathy, neuropathy, cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. A summary score representing the total number of diabetic complications was then created by summing each of these indicator variables. Diabetic complications were therefore incorporated into the analyses as a continuous variable with a potential range of 0 to 6.

Behavioral Health Services Status

An integrated behavioral health services program is provided to primary care patients receiving medical care with the CommUnityCare clinics. Individuals may receive these services based on the referral of their primary care provider. Examples of reasons for referral to the integrated behavioral health program include medication management assistance, instruction on self-management of behavioral health conditions, and other issues related to behavioral healthcare. These services are provided by trained behavioral health consultants and psychiatrists who operate in collaboration with the patient's primary care provider. Behavioral health interventions typically consist of five to six behavioral health encounters occurring over a variable time period.

In order to control for the effect of receiving these specialized behavioral health services on any of the outcomes evaluated in this study, behavioral health services status was incorporated as a covariate in the regression models for Objective 3, Objective 4, and Objective 5. For these analyses, individuals were coded as receiving behavioral health services if they displayed one of the relevant Current Procedural Terminology (CPT) codes at any encounter during the observation period. Behavioral health services status was coded as 1 if an individual had any of the following CPT codes associated with a clinic encounter:

- 90801 (Psychiatric diagnostic interview examination);
- 90804 (Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 20 to 30 minutes face-to-face with the patient); or
- 90805 (Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 20 to 30 minutes face-to-face with the patient; with medical evaluation and management services).

DATA ANALYSIS

The purpose of this section is to describe the analytic methods and procedures that were employed for this study. The analytic approach and methods are described for each objective and the related hypotheses. The *a priori* alpha level for all analyses was set at 0.05, and all statistical tests were two-tailed. Data were evaluated for violations of assumptions (e.g., presence of multicollinearity, violation of the proportional hazard assumption) underlying the associated statistical tests. All statistical analyses were conducted using PASW version 18.0.

Objective 1

Cohort Construction

The purpose of Objective 1 (Table 2.1) is to evaluate diabetes as a risk factor for incident depression among a cohort of indigent primary care patients. The analytic cohort for this objective was constructed by identifying individuals with continuous clinic eligibility for a period of 24 months, after removing subjects receiving reproductive healthcare services and family planning services. The latter subjects were excluded from these analyses due to the large number of subjects receiving only reproductive healthcare services within the clinics, and to remove potential bias that inclusion of these subjects may have introduced. For the purposes of the Objective 1 analyses, the initial 12-month period of service eligibility was considered the screening period, and the subsequent 12 months of service eligibility was considered the follow-up period.

Analytic Methods

For subjects meeting these requirements, encounters during the initial 12 months of clinic eligibility were inspected to identify diagnoses and clinical characteristics associated with these clinic encounters. In particular, the presence of diagnoses of diabetes and depression associated with encounters occurring during the 12-month screening period were identified. Individuals with a diagnosis indicative of diabetes or depression during the screening period were classified as prevalent cases of these conditions. Diagnostic data during the 12-month screening period were also utilized to calculate Charlson scores and to identify the presence and number of diabetic complications for subjects with a diagnosis of diabetes.

The follow-up period was defined as the 12 months of clinic service following the 12-month screening period. Diagnostic data associated with clinic encounters during the 12-month follow-up period were screened for the presence of diagnoses of diabetes or depression in a manner similar to that used for the screening period.

The prevalence of diabetes and depression was calculated as the total number of cases of the respective disorder during the screening period divided by the total number of subjects included in the analysis. The 12-month incidence of diabetes during the follow-up period was calculated as the total number of new cases of diabetes during the follow-up period divided by the number of subjects without a diagnosis of prevalent diabetes during the screening period. The 12-month incidence of depression was calculated in a similar manner, with the denominator representing the number of individuals without a diagnosis of prevalent depression during the screening period.

In order to evaluate the association between diabetes diagnostic status and incident diagnosis of depression, the analytic dataset for Hypothesis 1.1 and Hypothesis

1.2 was limited to individuals who did not display a prevalent diagnosis of depression during the screening period.

Hypothesis 1.1 evaluated the bivariate association between prevalent diabetes and incident depression during the 12-month evaluation period. Hypothesis 1.1 was formally tested via bivariate logistic regression of depression diagnostic status on prevalent diabetes diagnostic status. Hypothesis 1.2 evaluated the association between prevalent diabetes and incident depression, after statistically controlling for the influence of covariates as previously described. Hypothesis 1.2 was tested by multivariate logistic regression of incident depression diagnostic status on diabetes diagnostic status with the inclusion of the following covariates: age, gender, race/ethnicity, marital status, and Charlson score. For each variable included in both logistic regression models, the regression coefficient, the standard error of the regression coefficient, the Wald statistic and associated p-value, as well as the odds ratio with 95% confidence interval are reported.

Table 2.1 Hypotheses, related study variables, and statistical tests for Objective 1

Hypothesis	Independent Variable		Dependent Variable		Covariates	Statistical Test
	Variable Name	Variable Type	Variable Name	Variable Type		
Objective 1. Evaluate diabetes as a risk factor for depression among indigent primary care patients.						
H_0 1.1	Diabetes diagnostic status	Dichotomous	Depression diagnostic status	Dichotomous	N/A	Bivariate logistic regression
H_0 1.2	Diabetes diagnostic status	Dichotomous	Depression diagnostic status	Dichotomous	Age Gender Ethnicity Marital Status Charlson score	Multivariate logistic regression

N/A, not applicable

Objective 2

Cohort Construction

The purpose of Objective 2 (Table 2.2) is to evaluate risk factors for an incident diagnosis of depression among subjects with pre-existing diabetes. The analytic cohort for this objective was identical to that used for Objective 1 with the additional requirement that all members of the cohort display a prevalent diagnosis of diabetes during the screening period. This cohort of diabetic patients without prevalent depression was followed for 12 months after the initial 12-month screening period. Cases of incident depression were identified during the 12-month follow-up period using the same methodology as described for Objective 1.

Hemoglobin A1c laboratory data obtained during the screening period were incorporated as a variable in the analysis related to Objective 2. A total of 179 of 2394 subjects included in the cohort for Objective 2 had one or more HbA1c labs reported during the screening period. In the case where an individual had only a single HbA1c value during the screening period, that data was incorporated into the analysis without regard to the time point that the laboratory value was obtained. For individuals with multiple HbA1c laboratory values during the screening period, the laboratory test closest to the end of the screening period was utilized in the analysis.

Analytic Methods

A multivariate logistic regression model incorporating the variables of interest was constructed. The purpose of this analysis was to evaluate the association between individual predictors while controlling for the influence of other variables included in the model. This analysis was conducted by regressing incident depression diagnostic status

on the following variables simultaneously: age, gender, race/ethnicity, marital status, hemoglobin A1c value, number of diabetic complications, and Charlson score. This multivariate logistic regression model was used to test the specific hypotheses related to Objective 2.

Table 2.2 Hypotheses, related study variables, and statistical tests for Objective 2

Hypothesis	Independent Variable		Dependent Variable		Statistical Test
	Variable Name	Variable Type	Variable Name	Variable Type	
Objective 2. Evaluate risk factors for an incident diagnosis of depression among patients diagnosed with prevalent diabetes.					
H_0 2.1	Age	Continuous	Depression status	Dichotomous	Multivariate logistic regression
H_0 2.2	Gender	Categorical	Depression status	Dichotomous	Multivariate logistic regression
H_0 2.3	Ethnicity	Categorical	Depression status	Dichotomous	Multivariate logistic regression
H_0 2.4	Marital status	Categorical	Depression status	Dichotomous	Multivariate logistic regression
H_0 2.5	Hemoglobin A1c value	Continuous	Depression status	Dichotomous	Multivariate logistic regression
H_0 2.6	No. diabetic complications	Continuous	Depression status	Dichotomous	Multivariate logistic regression
H_0 2.7	Charlson score	Continuous	Depression status	Dichotomous	Multivariate logistic regression

Covariates for H_0 2.1-2.7: Age, gender, race/ethnicity classification, marital status classification, Hemoglobin A1c, number of diabetic complications, Charlson score.

Objective 3

Cohort Construction

The purpose of Objective 3 (Table 2.3) is to evaluate the association between a diagnosis of diabetes and antidepressant medication utilization patterns. The analytic cohort for this objective was constructed based on identification of an index event of an initial prescription for an antidepressant medication.

To construct this cohort, subjects with sufficient service eligibility and prescription claims records were screened for the presence of antidepressant prescription claims. The minimum possible length of continuous service eligibility required to be screened for inclusion in the cohort for Objective 3 was 18 months. A total of 49 subjects had 2 separate periods of service eligibility of 18-months or greater. In these 49 cases the most recent 18 month or greater eligibility period served as the evaluation period.

An initial antidepressant prescription was identified after performing a 6-month "look-back" for each antidepressant prescription claim screened. In order to qualify as an index antidepressant prescription, it was required that the antidepressant claim was preceded by a 6-month antidepressant-free interval. If there were no prescription claims for an antidepressant medication in the six months preceding the claim under review, the claim was considered an index antidepressant prescription, and the date associated with this prescription claim was treated as the index date. For subjects with an index antidepressant prescription, a 12-month "look-forward" was conducted to verify that the subject had 12 months of continuous clinic eligibility following the index date.

Once this initial group of subjects meeting the continuous eligibility requirement and having an index antidepressant prescription claim was constructed, one additional screen based on ICD-9 CM diagnostic codes took place. All subjects who had an ICD-9

CM diagnostic code for depression associated with any clinic encounter during the 18-month observation period (six months pre-index date and 12 months post-index date) were identified. All subjects without an ICD-9 CM code indicating a diagnosis of depression were excluded from the analytic dataset for Objective 3. This step was performed in order to identify individuals receiving antidepressant treatment for treatment of documented depression, as opposed to individuals using antidepressant medications for other indications (e.g., anxiety disorders). In a similar manner, individuals were classified with positive diabetes diagnostic status based on the presence of an ICD-9 CM diagnostic code at any point during the observation period.

Analytic Methods

Demographic and clinical characteristics of all subjects with an index event of an initial antidepressant prescription claim are reported. The diagnostic characteristics for these subjects in terms of frequency of depression diagnostic status and diabetes diagnostic status are likewise reported. The frequency of other psychiatric diagnoses associated with antidepressant use among the initial cohort of all subjects with an index antidepressant prescription claim is also reported.

After restriction of the cohort to only subjects with an observed diagnosis of depression, the simple frequency of class of antidepressant initially prescribed is reported, and these frequencies were compared in the group of patients with a diagnosis of diabetes to patients without a diagnosis of diabetes. Likewise, the clinical and demographic characteristics of subjects included in the final analytic cohorts are reported based on diabetes diagnostic status.

Hypothesis 3.1 was tested by means of logistic regression of initial class of antidepressant prescription on diabetes diagnostic status and the included covariates. Covariates incorporated into this model include: age, gender, ethnicity, marital status, behavioral health service status, and the Charlson score.

Hypotheses 3.2 and 3.3 evaluated the relationship between diabetes diagnostic status and antidepressant switch and discontinuation, respectively, during the 12-month follow-up period. These analyses were performed by means of logistic regression where the outcome (i.e., dichotomous indicator of switch or discontinuation, respectively) was the dependent variable. Diabetes diagnostic status was the independent variable of interest. Covariates incorporated into this model include: initial antidepressant class, age, gender, ethnicity, marital status, behavioral health services status, and the Charlson score.

Hypotheses 3.4 and 3.5 evaluated the association between diabetic diagnostic status and medication possession ratio. Six-month and 12-month MPR were calculated as previously described. The relationship between a diagnosis of diabetes and antidepressant adherence was evaluated via regression of antidepressant MPR on diabetes diagnostic status with appropriate covariates. Hypotheses 3.4 and 3.5 were tested using the generalized linear model procedure in PASW with a normal probability distribution and the identity link function.

Hypotheses 3.6 through 3.8 evaluate the relationship between diabetes diagnostic status and antidepressant medication persistence. Hypothesis 3.6 formally tested the relationship between diabetes diagnostic status and time to antidepressant non-persistence. The bivariate relationship between diabetes diagnostic status and time to antidepressant non-persistence was evaluated via Kaplan-Meier analysis and the difference between groups was tested with the log-rank test. Time to antidepressant non-persistence was evaluated via Cox proportional hazards regression with the inclusion of

appropriate covariates. The Cox proportional hazards regression model is a survival analysis technique that allows for modeling of time-to-event data in the presence of censored cases. Compared to the Kaplan-Meier analysis which evaluates survival time in a bivariate manner, the Cox model can be used to test the association between independent and dependent variables after controlling for the influence of covariates.

Hypotheses 3.7 and 3.8 evaluated the relationship between diabetes diagnostic status and persistence as a dichotomized variable at 3-month and 12-month time points. The relationships between diabetes diagnostic status and 3-month and 12-month antidepressant persistence were evaluated using logistic regression of persistence status on diabetes diagnostic status after controlling the influence of the included covariates. Covariates included in these models include: initial antidepressant class, age, gender, ethnicity, marital status, behavioral health services status, and the Charlson score.

Table 2.3 Hypotheses, related study variables, and statistical tests for Objective 3.

Hypothesis	Independent Variable		Dependent Variable		Statistical Test
	Variable Name	Variable Type	Variable Name	Variable Type	
Objective 3. Evaluate the association between diabetes diagnostic status and antidepressant medication utilization patterns.					
H_0 3.1	Diabetes status	Dichotomous	AD class	Dichotomous	Logistic regression
H_0 3.2	Diabetes status	Dichotomous	AD switch status	Dichotomous	Logistic regression
H_0 3.3	Diabetes status	Dichotomous	AD discontinuation status	Dichotomous	Logistic regression
H_0 3.4	Diabetes status	Dichotomous	6-month AD MPR	Continuous	Linear regression
H_0 3.5	Diabetes status	Dichotomous	12-month AD MPR	Continuous	Linear regression
H_0 3.6	Diabetes status	Dichotomous	Time to AD non-persistence	Continuous	Cox proportional hazards survival analysis
H_0 3.7	Diabetes status	Dichotomous	3-month AD persistence	Dichotomous	Logistic regression
H_0 3.8	Diabetes status	Dichotomous	12-month AD persistence	Dichotomous	Logistic regression

AD, antidepressant; DM, diabetes mellitus; MPR, medication possession ratio

Covariates for H_0 3.1: age, gender, ethnicity, marital status, Charlson score, behavioral health services status.

Covariates for H_0 3.2 through 3.8 : covariates for H0 3.1 model + initial antidepressant class.

Objective 4

Cohort Construction

The aim of Objective 4 (Table 2.4) is to evaluate the relationship between class of initial antidepressant treatment and antidepressant medication-taking behaviors in patients with diabetes receiving antidepressant treatment. In order to meet this objective, subjects with an index prescription claim for an antidepressant medication were identified in a method identical to that used to construct the cohort for Objective 3. Further, all subjects were required to have a diagnosis of diabetes. In order to preserve sufficient sample size, rather than limit the cohort to only individuals with a diagnosis of depression, depression diagnostic status was included as a covariate in all of the Objective 4 analyses. This was done in order to control for the influence of diverse indications for antidepressant treatment on the various outcomes of interest. In order to frame the interpretation of this included covariate in the intended fashion, the indicator for depression diagnostic status was reverse coded such that diagnosis of depression = 0, and the lack of a diagnosis of depression = 1. In addition to depression status, the number of diagnosed diabetic complications was included as a covariate for the statistical models used to test Hypotheses 4.1 to 4.7.

Analytic Methods

The statistical techniques used to test the hypotheses under Objective 4 were similar to those utilized to test Hypotheses 3.2 to 3.8. The primary difference between the analyses for Objective 4 and those included under Objective 3 were the analytic cohort being limited to subjects with a diagnosis of diabetes, inclusion of number of diabetic complications as a covariate, and the independent variable of interest.

Hypotheses 4.1 and 4.2 employed logistic regression to evaluate the association between class of antidepressant medication initially prescribed and antidepressant switch and discontinuation, respectively. Hypotheses 4.3 and 4.4 involved regression of 6- and 12-month antidepressant MPR, respectively, on class of initial AD medication. Hypothesis 4.5 evaluated the relationship between class of initial AD medication and time to antidepressant non-persistence via Cox proportional hazards survival analysis. Hypotheses 4.6 and 4.7 tested the relationship between initial AD class and 3- and 12-month AD persistence status, respectively, via the statistical technique of logistic regression. Covariates included in all of the models constructed to test the hypotheses under Objective 4 were: age, gender, ethnicity, marital status, number of diabetic complications, behavioral health services status, depression diagnostic status, and Charlson score.

Table 2.4 Hypotheses, related study variables, and statistical tests for Objective 4

Hypothesis	Independent Variable		Dependent Variable		Statistical Test
	Variable Name	Variable Type	Variable Name	Variable Type	
Objective 5. Evaluate the association between class of initial antidepressant medication treatment and antidepressant medication-taking behaviors in patients with type 2 diabetes and comorbid depression.					
H_0 4.1	AD class	Dichotomous	AD switch status	Dichotomous	Logistic regression
H_0 4.2	AD class	Dichotomous	AD discontinuation status	Dichotomous	Logistic regression
H_0 4.3	AD class	Dichotomous	6-month AD MPR	Continuous	Linear regression
H_0 4.4	AD class	Dichotomous	12-month AD MPR	Continuous	Linear regression
H_0 4.5	AD class	Dichotomous	Time to AD non-persistence	Continuous	Cox proportional hazards survival analysis
H_0 4.6	AD class	Dichotomous	3-month AD persistence status	Dichotomous	Logistic regression
H_0 4.7	AD class	Dichotomous	12-month AD persistence status	Dichotomous	Logistic regression

AD, antidepresant; MPR, medication possession ratio.
Covariates for H_0 4.1 - 4.7: age, gender, ethnicity, marital status, depression diagnostic status, number of diabetic complications, Charlson score, behavioral health services status.

Objective 5

Cohort Construction

The purpose of Objective 5 (Table 2.5) is to evaluate the relationship between antidepressant adherence and glycemic control, as measured by HbA1c value. The analytic cohort for this objective consisted of subjects with an index antidepressant prescription (identified as previously described for Objective 3) and available HbA1c laboratory data during the follow-up period.

Analytic Methods

A limited number of subjects had HbA1c data that could be incorporated into the analyses under Objective 5. In order to build a cohort of sufficient size, very limited restrictions were placed on the allowable timeframe for incorporation of HbA1c data. While the HbA1c values reflect glycemic control over a period of approximately 120 days preceding measurement, HbA1c were incorporated for all subjects over a broad period of follow-up. HbA1c data were incorporated, as available, for any subject with an HbA1c measurement after the index event of an initial antidepressant prescription, extending beyond the 12-month terminus of the predefined follow-up period. In the case where an individual had only a single HbA1c lab after the index date, that data was incorporated into the analysis without regard to the time point that the laboratory value was obtained. For individuals with multiple HbA1c labs after the index antidepressant claim, the laboratory value obtained at the time point closest to the end of 12-month post index observation period was utilized in the analysis. In addition, the lack of HbA1c laboratory data for subjects during the pre-index screening period necessitated the removal of pre-index HbA1c as a covariate for inclusion in the Objective 5 analyses.

These methodological limitations, necessary due to limited data availability, are acknowledged as a threat the internal validity of the analyses conducted to test Hypotheses 5.1 and 5.2. The temporal distribution of HbA1c data utilized for Objective 5 analyses is presented in the results section.

Hypotheses 5.1 and 5.2 were tested using the generalized linear model procedure with a normal probability distribution and the identity link function. Regression of HbA1c values on antidepressant MPR was conducted with age, gender, ethnicity, marital status, and Charlson score included as covariates.

Table 2.5 Hypotheses, related study variables, and statistical tests for Objective 5

Hypothesis	Independent Variable		Dependent Variable		Statistical Test
	Variable Name	Variable Type	Variable Name	Variable Type	
Objective 5. Evaluate the relationship between antidepressant medication adherence and glycemic control.					
H_0 5.1	6-month AD MPR	Continuous	HbA1c	Continuous	Linear regression
H_0 5.2	12-month AD MPR	Continuous	HbA1c	Continuous	Linear regression

AD, antidepressant; DM, diabetes mellitus; MPR, medication possession ratio; HbA1c, hemoglobin A1c

Covariates for H_0 5.1-5.2: age, gender, ethnicity, martial status, behavioral health service status, Charlson score.

Power Calculations

A series of calculations were conducted prior to constructing the study cohorts in order to estimate the power of the proposed statistical analyses based on a number of assumptions regarding the data. For all power calculations, the alpha-level (probability of a type I error) was set to 0.050 and a two-tailed distribution was used. A number of assumptions regarding the sample size were made in order to estimate the power of certain statistical analyses; therefore, the preliminary analyses presented here were treated as *a priori* power estimates rather than sample size calculations.

It was initially estimated that there would be data available for 10,000 unique subjects for analysis. Based on conservative prevalence estimates for diabetes and depression of 10% each, it was anticipated that approximately 1,000 subjects with diabetes and 1,000 subjects with depression would be identified. Of these 1,000 subjects with diabetes, for the purpose of these preliminary power estimates, it was estimated that approximately 200 subjects (20%) would have comorbid diabetes and major depression. An incidence rate of 20 new cases of depression per 1,000 patient-years among individuals with diabetes, and 10 incident cases per 1,000 patient-years among non-diabetics was estimated. Based on these assumptions regarding sample size, power estimates for the analyses associated with select study hypotheses were conducted with SPSS Sample Power 2.0 and are summarized in Table 2.6.

Table 2.6 Power estimates for select hypotheses and related statistical tests

Hypothesis	Statistical Test	Power Estimate
H_0 1.1	Logistic regression	Power of 0.99 to detect a 2-fold difference in the incidence of depression for subjects with a diagnosis of diabetes compared to those without a diagnosis of diabetes.
H_0 3.4	Linear regression	Power of 0.99 to detect a 0.05 increment to R-squared for the primary variable of interest (diagnosis of major depression).
H_0 4.7	Logistic regression	Power of 0.70 to detect a difference of 20% in 12-month persistence status for subjects receiving SSRI vs. SNRI and atypical antidepressant treatment.

All estimates are based on an alpha-level of 0.050, estimated overall sample size of 10,000, prevalence of diabetes of 10%, prevalence of depression of 10%, prevalence of depression among individuals with depression of 20%, and incidence of depression of 20 and 10 per 1000 pt-years for patients with diabetes and non-diabetics, respectively. All calculations were performed using SPSS Sample Power 2.0.

Chapter 3: Results

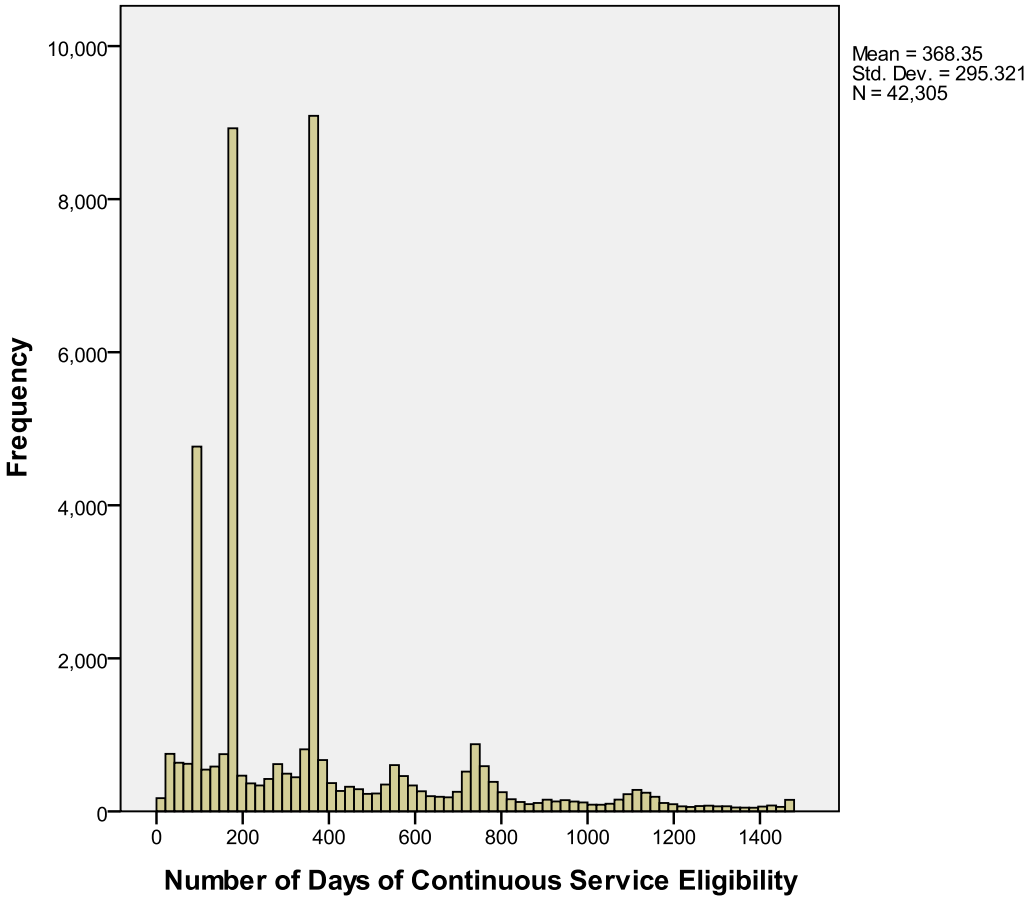
Chapter Overview

The purpose of this chapter is to present the results of this research. This chapter is organized by objective, with results related to the analysis of each hypothesis summarized.

Data Extraction and Case Identification

Data were extracted for 34,152 subjects who met the criteria for data extraction. These subjects had a total of 42,305 unique continuous eligibility periods. The distribution of days of service eligibility was tri-modal at 90, 180 and 365 days (Figure 3.1). The mean, median, and mode of the number of days of continuous service eligibility were 368.4 days (± 295.3), 341.0 days (interquartile range: 229), and 365 days, respectively. Among these 42,305 unique continuous eligibility periods, 8,699 (20.6%) and 5,743 (13.6%) had continuous service eligibility periods of greater than or equal to 18 and 24 months, respectively.

Figure 3.1 Distribution of number of days of continuous service eligibility for subjects meeting data extraction criteria



OBJECTIVE 1

Purpose

The purpose of Objective 1 was to evaluate diabetes diagnostic status as a risk factor for incident diagnosis of depression. There were two formal hypotheses tested in relationship to Objective 1.

Cohort Description

Among the 34,152 subjects with eligibility data, total of 2,886 subjects met the criteria for inclusion in the objective 1 analytic cohort. The demographic characteristics of these subjects are presented in Table 3.1. Overall, subjects were predominantly female (72.8%) and classified as White Hispanic (73.5%). In terms of marital status, classification as married (37.0%) and single (30.5%) were most common, with a substantial proportion of patients displaying missing data or a classification as unknown, unreported, or missing (27.1%).

Diabetes and depression diagnostic status for the 2,886 subjects included in this analysis are presented in Table 3.2. Seven hundred and sixty four (26.5%) subjects displayed a diagnosis of diabetes during the 12-month screening period. Among these subjects, the mean number of diabetic complications was 0.20 ± 1.95. The mean Charlson score for these subjects with diabetes during the screening period was 1.36 ± 0.66. Of the 764 subjects with a diagnosis of diabetes, 206 subjects had HbA1c laboratory test data available. The mean HbA1c value for these subjects was 7.86 ± 1.95. A total of 2,122 subjects did not exhibit a diagnosis of diabetes during the 12-month screening period. The 12-month incidence of diabetes during the 12-month follow-up period was 3.8%

(n=81). The number of subjects who did not display a diagnosis of diabetes during either the 12-month screening period or the 12-month follow-up period was 2,041 (70.7%).

Table 3.1 Summary of demographic characteristics for subjects with 24 months of continuous service eligibility

Variable	n	(%)
Gender		
Female	2,101	(72.8%)
Male	785	(27.2%)
Total	2,886	(100.0%)
Race/ethnicity		
White (Hispanic)	2,122	(73.5%)
White (non-Hispanic)	394	(13.7%)
Black/African-American	210	(7.3%)
Other†	92	(3.2%)
Unknown‡	68	(2.4%)
Total	2,886	(100.0%)
Marital status		
Single	879	(30.5%)
Married	1,068	(37.0%)
Divorced	74	(2.6%)
Widowed	47	(1.6%)
Legally separated	36	(1.2%)
Life partner	1	(0.0%)
Unknown‡	781	(27.1%)
Total	2,886	(100.0%)

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian.
‡ Unknown includes unknown, unreported, and missing.

Of the 2,886 subjects initially identified, 492 (17.0%) subjects were identified who had a diagnosis of depression during the screening period (Table 3.2). There were 2,394 subjects who did not have a diagnosis of depression during the screening period. The 12-month incidence of depression in the overall cohort was 6.8% (n = 163). A total

of 2,231 (77.3%) subjects did not have a diagnosis of depression during either the 12-month screening period or the 12-month follow-up period.

Table 3.2 Depression and diabetes status for subjects identified by study inclusion criteria

Variable	n	(%)
Depression Status		
No depression during observation period	2,231	(77.3%)
Prevalent depression†	492	(17.0%)
New-onset depression‡	163	(5.6%)
Total	2,886	(100.0%)
Diabetes Status		
No diabetes during observation period	2,041	(70.7%)
Prevalent diabetes†	764	(26.5%)
New-onset diabetes‡	81	(2.8%)
Total	2,886	(100.0%)

† Number of subjects displaying a diagnosis during the screening period

‡ Number of subjects displaying a diagnosis during the follow-up period but not the screening period

In order to evaluate the association between diabetes diagnostic status and incident diagnosis of depression, individuals with a prevalent diagnosis of depression (n = 492) were removed from the analytic dataset for analyses for Hypotheses 1.1 and 1.2. This left 2,394 subjects eligible for inclusion in the analyses related to these hypotheses.

Hypothesis 1.1

H_0 1.1: There is no statistically significant association between diabetes diagnostic status and incident depression diagnostic status among indigent primary care patients.

Logistic regression was used to evaluate the bivariate relationship between prevalent diabetes and incident depression. The raw incidence of depression among patients with a diagnosis of diabetes was 5.2 percent (n = 34) and among patients without a diagnosis of diabetes the incidence was 7.4 percent (n = 129). Results of the regression model evaluating the bivariate association between diabetes and incident depression are presented in Table 3.3.

Table 3.3 Bivariate logistic regression of depression diagnostic status on diabetes diagnostic status

Variable	B	SE	Wald	p-value	OR	95% CI	
Prevalent diabetes status	-0.38	0.20	3.59	0.058	0.69	0.05	1.01
Constant	-2.53	0.09	761.77	**< 0.001**	0.08		

Dependent variable: incident depression status: 0, not present; 1, present.

Model $\chi^2 = 3.824$, df = 1, p = 0.051

n = 2394

In the bivariate analysis, the presence of prevalent diabetes was not associated with incident depression at a statistically significant level (B = -0.38, p = 0.058, OR 0.69, 95% CI 0.05-1.01). While the results did not achieve statistical significance, the direction of the association indicated a trend towards reduced odds of displaying a diagnosis of incident depression for individuals diagnosed with diabetes at baseline. Based on these results, H_0 1.1 was not rejected.

Exploratory Analyses

Post-hoc exploratory analyses were conducted to evaluate the association between prevalent diabetes and prevalent depression across the study period. These analyses were performed in order to evaluate the cross-sectional relationship between depression and diabetes during different timeframes. These analyses differed from the *a priori* analysis in that the relationship was evaluated in terms of prevalent cases, as opposed to incident cases. Three timeframes were used for identification of prevalent cases: 12-month screening period, 12-month follow-up period, and the overall 24-month evaluation period.

The crosstabulations of depression status by diabetes status for each timeframe are presented in Tables 3.4, 3.5, and 3.6. The prevalence of depression among subjects with a diagnosis of diabetes was lower when compared to non-diabetic subjects during all evaluation periods. The prevalence of diabetes among subjects diagnosed with depression was lower when compared to subjects without depression for each time period evaluated. The Phi correlation coefficient between prevalent diabetes and prevalent depression was low, negative, and statistically significant for all timeframes evaluated (n = 2886, screening period: $r_{\varphi} = -0.040$, p = 0.031; follow-up period: $r_{\varphi} = -0.054$, p = 0.004; overall timeframe: $r_{\varphi} = -0.041$, p = 0.026).

Table 3.4 Crosstabulation of depression status by diabetes status for 12-month screening period

Depression Status	Diabetes Status: Absent n	Absent Column %	Absent Row %	Present n	Present Column %	Present Row %	Row Total	
Absent	1741	(82.0%)	(72.7%)	653	(85.5%)	(27.3%)	2394	(83.0%)
Present	381	(18.0%)	(77.4%)	111	(14.5%)	(22.6%)	492	(17.0%)
Col. Total	2122	(73.5%)		764	(26.5%)		2886	(100.0%)

$\chi^2 = 4.662$, df = 1, p = 0.031

Table 3.5 Crosstabulation of depression status by diabetes status for 12-month follow-up period

Depression Status	Diabetes Status: Absent n	Absent Column %	Absent Row %	Present n	Present Column %	Present Row %	Row Total	
Absent	1751	(84.0%)	(71.2%)	708	(88.3%)	(28.8%)	2459	(85.2%)
Present	333	(16.0%)	(78.0%)	94	(11.7%)	(22.0%)	427	(14.8%)
Col. Total	2084	(72.2%)		802	(27.8%)		2886	(100.0%)

$\chi^2 = 8.330$, df = 1, p = 0.004

Table 3.6 Crosstabulation of depression status by diabetes status for overall 24-month evaluation period

Depression Status	Diabetes Status: Absent n	Absent Column %	Absent Row %	Present n	Present Column %	Present Row %	Row Total	
Absent	1555	(76.2%)	(69.7%)	676	(80.0%)	(30.3%)	2231	(77.3%)
Present	486	(23.8%)	(74.2%)	169	(20.0%)	(25.8%)	655	(22.7%)
Col. Total	2041	(70.7%)		845	(29.3%)		2886	(100.0%)

$\chi^2 = 4.949$ df = 1, p = 0.026

Hypothesis 1.2

H_0 1.2: After controlling for age, gender, race/ethnicity, marital status, and Charlson score there is no statistically significant association between diabetes diagnostic status and incident depression diagnostic status among indigent primary care patients.

In addition to evaluation of the bivariate relationship between prevalent diabetes and incident depression, a multivariate analysis was conducted evaluating this relationship while controlling for the influence of covariates. Covariates included in the model were age, gender, race/ethnicity, marital status, and Charlson score. Descriptive statistics for covariates included in the model are presented in Table 3.7.

Results of the multivariate logistic regression analysis are presented in Table 3.8. After controlling for age, gender, race/ethnicity, marital status, and Charlson score, prevalent diabetes was associated with a lower odds of diagnosis of incident depression (B = -0.54, p = 0.021, OR 0.58 95%, CI 0.37 to 0.92). These results indicate that the presence of a diagnosis of prevalent diabetes is associated with a reduction in the odds of an individual displaying an incident diagnosis of depression during the 12-month follow-up period by 42 percent.

Among the covariates included in this model, age (B = 0.22, p = 0.007, OR 1.02, 95% CI 1.01 to 1.04), male gender (B = -0.51, p = 0.014, OR 0.60, 95% CI 0.40 to 0.90), White non-Hispanic race/ethnicity (B = 1.18, p <0.001, OR 3.24, 95% CI 2.13 to 4.94) as well as divorced, widowed, or other marital status (B = -0.69, p = 0.001, OR 0.50, 95% CI 0.33 to 0.76) were associated with incident depression diagnostic status at a statistically significant level. Each year increase in age was associated with a 2 percent

Table 3.7 Descriptive statistics for age, gender, race/ethnicity, marital status and Charlson score for subjects included in analyses related to Hypothesis 1.2

Variable	Diabetes prevalent n=653		Diabetes not prevalent n=1,741	
Age (mean, SD)	49.12	(11.68)	41.03	(9.69)
Gender (n, %)				
Female	439	(67.2%)	1,282	(73.6%)
Male	214	(32.8%)	459	(26.4%)
Total	653	(100.0%)	1,741	(100.0%)
Race/ethnicity (n, %)				
White (Hispanic)	511	(78.3%)	1,308	(75.1%)
White (non-Hispanic)	54	(8.3%)	200	(11.5%)
Black/African-American	63	(9.6%)	119	(6.8%)
Other or Unknown†	25	(3.8%)	114	(6.5%)
Total	653	(100.0%)	1,741	(100.0%)
Marital status (n, %)				
Single	214	(32.8%)	496	(28.5%)
Married	230	(35.2%)	702	(40.3%)
Other or unknown‡	209	(32.0%)	543	(31.2%)
Total	653	(100.0%)	1,741	(100.0%)
Charlson score (mean, SD)	1.36	(0.68)	0.20	(0.80)

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian. Unknown includes unknown, unreported, and missing.

‡ Other included divorced, widowed, legally separated, and life partner. Unknown includes missing and unknown.

Table 3.8 Logistic regression of depression diagnostic status on diabetes diagnostic status after controlling for age, gender, race/ethnicity classification, marital status classification, and Charlson score

Variable	B	SE	Wald	p-value	OR	95% CI	
Prevalent diabetes status	-0.54	0.23	5.39	**0.021**	0.58	0.37	0.92
Age	0.22	0.01	7.21	**0.007**	1.02	1.01	1.04
Male gender	-0.51	0.21	6.02	**0.014**	0.60	0.40	0.90
White non-Hispanic	1.18	0.22	29.98	**< 0.001**	3.24	2.13	4.94
African-American	0.76	0.32	0.57	0.811	1.08	0.58	2.01
Other race/ethnicity	0.29	0.36	0.67	0.414	1.34	0.67	2.68
Married	-0.32	0.20	2.61	0.106	0.72	0.49	1.07
Divorced, widowed, or other	-0.69	0.21	10.53	**0.001**	0.50	0.33	0.76
Charlson score	0.09	0.09	0.87	0.351	1.09	0.91	1.31
Constant	-2.78	0.45	37.69	**< 0.001**	0.06		

Dependent variable: Incident Depression Status: 0, not present; 1, present.

Model $\chi^2 = 67.256$, df = 9, $p < 0.001$

n = 2394

Comparison group for race/ethnicity classifications is White Hispanic; comparison group for marital status classifications is Single.

increase in the odds of diagnosis of incident depression. Male gender was associated with a 40 percent reduced odds of incident diagnosis of depression compared to female gender. Relative to subjects classified as White Hispanic, subjects classified as White non-Hispanic had a 3.24-fold increased probability of being diagnosed with incident depression. Finally, marital status classification as divorced, widowed, other, or unknown was associated with a 50 percent decrease in the odds of being diagnosed with incident depression during the 12-month follow-up period. H_0 1.2 is rejected based on these results.

Summary

The results of analyses related to Objective 1 are summarized in Table 3.9. Based on the results of analyses as described in this section, H_0 1.1 was not rejected. H_0 1.2 was rejected based on the statistically significant association between diabetes diagnostic status and incident depression status in the multivariate model. The results of the multivariate logistic regression model indicate that a diagnosis of diabetes is associated with decreased likelihood of observing an incident diagnosis of depression in this cohort of indigent care patients.

Table 3.9 Summary of hypothesis testing related to Objective 1

Hypothesis	Independent Variable		Dependent Variable		Covariates	Statistical Test	Result
	Variable Name	Variable Type	Variable Name	Variable Type			
Objective 1. Evaluate diabetes as a risk factor for depression among indigent primary care patients.							
H_0 1.1	Diabetes diagnostic status	Dichotomous	Depression diagnostic status	Dichotomous	N/A	Bivariate logistic regression	Failed to reject
H_0 1.2	Diabetes diagnostic status	Dichotomous	Depression diagnostic status	Dichotomous	Age Gender Ethnicity Marital Status Comorbidity index	Multivariate logistic regression	Rejected

N/A, not applicable

OBJECTIVE 2

Purpose

The purpose of Objective 2 was to evaluate the association between demographic and clinical factors and incident depression among patients diagnosed with diabetes. There were seven formal hypotheses tested in relationship to Objective 2.

Cohort description

The analytic cohort for Objective 2 was based on the cohort utilized for analysis of hypotheses 1.1 and 1.2, with the additional restriction that all subjects display prevalent diabetes during the screening period. This procedure resulted in the identification of 653 subjects eligible for inclusion in the Objective 2 analysis. Further, the requirement that HbA1c values obtained during the screening period were available for analysis reduced the analytic cohort to 179 subjects. Among these 179 subjects there were 7 (3.9%) cases of new-onset depression during the 12 months of follow-up. The demographic and clinical characteristics of these patients are presented in Table 3.10.

Table 3.10 Demographic and clinical characteristics of 179 subjects with a prevalent diagnosis of diabetes, no diagnosis of depression during the screening period, and available hemoglobin A1c data

Variable		
Age (mean, SD)	49.37	(10.00)
Gender (n, %)		
Female	121	(67.6%)
Male	58	(32.4%)
Total	179	(100.0%)
Race/ethnicity (n, %)		
White (Hispanic)	142	(79.3%)
White (non-Hispanic)	8	(4.5%)
Black/African-American	21	(11.7%)
Other†	4	(2.2%)
Unknown‡	4	(2.2%)
Total	179	(100.0%)
Marital status (n, %)		
Single	56	(31.3%)
Married	64	(35.8%)
Divorced	6	(3.4%)
Widowed	8	(4.5%)
Legally separated	4	(2.2%)
Unknown‡	41	(22.9%)
Total	179	(100.0%)
Charlson Score (mean, SD)	1.31	(0.06)
Hemoglobin A1c (mean, SD)	7.68	(1.89)
No. diabetic complications (mean, SD)	0.21	(0.47)

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian.

‡ Unknown includes unknown, unreported, and missing.

Hypotheses 2.1 to 2.7

H_0 2.1: After controlling for the influence of covariates, there is no statistically significant association between **age** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 2.2: After controlling for the influence of covariates, there is no statistically significant association between **gender** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 2.3: After controlling for the influence of covariates, there is no statistically significant association between **race/ethnicity** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 2.4: After controlling for the influence of covariates, there is no statistically significant association between **marital status** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 2.5: After controlling for the influence of covariates, there is no statistically significant association between baseline **HbA1c level** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 2.6: After controlling for the influence of covariates, there is no statistically significant association between the **diabetic complications** and depression diagnostic status in patients with a diagnosis of diabetes.

H_0 2.7: After controlling for the influence of covariates, there is no statistically significant association between the **Charlson score** and depression diagnostic status in patients with a diagnosis of diabetes.

Hypotheses 2.1-2.7 were evaluated by means of multivariate logistic regression with incident depression diagnostic status as the dependent variable. Age, gender, ethnicity, marital status, HbA1c, number of diabetic complications present, and the Charlson score were simultaneously entered into the regression model. The results of the multivariate model are presented in Table 3.11. None of the variables included in the model demonstrated a statistically significant association with diagnosis of incident depression. Among the variables included in the model, only age (B = -0.08, p = 0.093, OR 0.92, 95% CI 0.84 to 1.01) and African-American race/ethnicity (B = 1.71, p = 0.086, OR 5.51, 95% CI 0.79 to 38.67) were associated with a p-value < 0.10. Therefore, H_0 2.1 through H_0 2.7 were not rejected.

Table 3.11 Logistic regression of incident depression diagnostic status on age, gender, race/ethnicity classification, marital status classification, hemoglobin A1c, number of diabetic complications, and Charlson score in a cohort of subjects with prevalent diabetes

Variable	B	SE	Wald	p-value	OR	95% CI	
Age	-0.08	0.05	2.82	0.093	0.92	0.84	1.01
Male gender	-1.05	1.17	0.80	0.370	0.35	0.04	3.48
White non-Hispanic	-18.58	12381.74	< 0 .01	0.999	0.00	NR	NR
African-American	1.71	0.99	2.95	0.086	5.51	0.79	38.67
Other race/ethnicity	1.73	1.45	1.42	0.233	5.63	0.33	96.11
Married	0.35	1.05	0.11	0.739	1.42	0.18	11.17
Divorced, widowed, or other	0.31	1.15	0.07	0.785	1.37	0.14	13.13
Hemoglobin A1c	-0.10	0.21	0.23	0.628	0.90	0.60	1.36
No. diabetic complications	0.33	1.04	0.10	0.752	1.39	0.18	10.72
Charlson score	0.43	0.69	0.39	0.532	1.54	0.40	6.03
Constant	0.11	3.09	0.00	0.972	1.11		

Dependent variable: Incident Depression Status: 0, not present; 1, present.

Model $\chi^2 = 9.289$, df = 10, p = 0.505

n = 179

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

NR, not reported

Exploratory Analyses

Post-hoc exploratory analyses were conducted to evaluate factors associated with a prevalent diagnosis of depression among subjects with a prevalent diagnosis of diabetes. Individuals were classified as having diabetes and/or depression if they demonstrated a diagnostic code for either disorder at any point over the 24-month timeframe. Depression diagnostic status was regressed on age, gender, ethnicity, marital status, and Charlson score for patients with a diagnosis of diabetes. HbA1c value was not incorporated in this exploratory analysis due to the impact on sample size. A total of 845 subjects with a diagnosis of diabetes during the 24-month observation timeframe were identified. This regression analysis revealed a statistically significant association between male gender and depression diagnostic status (B = -0.63, p = 0.003, OR 0.53, 95% CI 0.35 to 0.81), and White non-Hispanic race/ethnicity and depression diagnostic status (B = 1.15, p < 0.001, OR 3.16, 95% CI 1.95 to 5.13) (Table 3.12). None of the other variables included in the exploratory analysis achieved statistical significance.

Table 3.12 Logistic regression of depression diagnostic status on age, gender, race/ethnicity classification, marital status classification, number of diabetic complications, and Charlson score in a cohort of subjects with prevalent diabetes

Variable	B	SE	Wald	p-value	OR	95% CI	
Age	< 0.01	0.01	0.27	0.606	1.00	0.99	1.02
Male gender	-0.63	0.22	8.56	**0.003**	0.53	0.35	0.81
White non-Hispanic	1.15	0.25	21.71	**< 0.001**	3.16	1.95	5.13
African-American	-0.44	0.38	1.36	0.243	0.64	0.31	1.35
Other race/ethnicity	-0.22	0.51	0.18	0.673	0.81	0.30	2.19
Married	-0.18	0.23	0.60	0.438	0.83	0.53	1.32
Divorced, widowed, or other	0.36	0.22	2.77	0.096	1.43	0.94	2.18
No. diabetic complications	0.21	0.24	0.75	0.386	1.23	0.77	1.96
Charlson score	-0.13	0.14	0.85	0.355	0.88	0.66	1.16
Constant	-0.91	0.57	2.55	0.111	0.40		

Dependent variable: Incident Depression Status: 0, not present; 1, present.

Model $\chi^2 = 44.915$, df = 9, p = < 0.001

n = 845

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Summary

The results of the tests of hypotheses 2.1 through 2.7 are summarized in Table 3.13. Age, gender, race/ethnicity, marital status, HbA1c value, number of diabetic complications, and comorbidity score were evaluated for their association with an incident diagnosis of depression among diabetic subjects. None of the factors evaluated were associated with incident diagnosis of depression. Based on the results of this analysis, H_0 2.1 through H_0 2.7 were not rejected. Post-hoc exploratory analysis revealed that female gender and White non-Hispanic race/ethnicity were associated with increased odds of prevalent diagnosis of depression among subjects with a diagnosis of diabetes.

Table 3.13 Summary of hypothesis testing related to Objective 2

Hypothesis	Independent Variable		Dependent Variable		Statistical Test	Result
	Variable Name	Variable Type	Variable Name	Variable Type		
Objective 2. Evaluate risk factors for an incident diagnosis of depression among patients diagnosed with prevalent diabetes.						
H_0 2.1	Age	Continuous	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject
H_0 2.2	Gender	Categorical	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject
H_0 2.3	Ethnicity	Categorical	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject
H_0 2.4	Marital status	Categorical	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject
H_0 2.5	Hemoglobin A1c value	Continuous	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject
H_0 2.6	No. diabetic complications	Continuous	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject
H_0 2.7	Charlson score	Continuous	Depression status	Dichotomous	Multivariate logistic regression	Failed to Reject

Covariates for H_0 2.1-2.7: Age, gender, race/ethnicity classification, marital status classification, Hemoglobin A1c, number of diabetic complications, Charlson score.

OBJECTIVE 3

Purpose

The purpose of Objective 3 is to evaluate the association between diabetes diagnostic status and antidepressant medication utilization patterns among subjects with a diagnosis of depression. There were eight formal hypotheses tested in relationship to Objective 3.

Cohort Description

Individuals were identified for inclusion in the analytic cohort for Objective 3 based on continuous service eligibility and antidepressant exposure, as described in Chapter 2. Based on these procedures, 455 subjects were identified with an index antidepressant prescription claim and sufficient continuous clinic service.

Demographic characteristics for these subjects are presented in Table 3.14. This cohort was primarily female (83.1%). In terms of race/ethnicity, the cohort was predominantly classified as White Hispanic (73.2%). The distribution of marital status was relatively balanced between single (36.5%), married (37.4%), and other/unknown (26.1%). A total of 205 subjects (45.1%) received specialized behavioral health services within the clinics.

The frequency of type of antidepressant medication at index is presented in Table 3.15. The most frequently observed index antidepressant medications were from the SSRI class: sertraline (49.5%), fluoxetine (13.0%), escitalopram (13.4%), and paroxetine (6.6%). Among the SNRI medications, the overall frequency was 5.7 percent for duloxetine and 3.3 percent for venlafaxine. The atypical antidepressants bupropion and

mirtazapine were observed for 5.3 percent and 1.1 percent of index antidepressant claims, respectively.

Table 3.14 Demographic characteristics for subjects meeting continuous service eligibility criteria and having an index prescription claim for an antidepressant medication

Variable		n	(%)
Gender			
	Female	378	83.1%
	Male	77	16.9%
	Total	455	100.0%
Race/Ethnicity			
	White (Hispanic)	333	73.2%
	White (non-Hispanic)	75	16.5%
	Black/African American	31	6.8%
	Other†	6	1.3%
	Unknown‡	10	2.2%
	Total	455	100.0%
Marital Status			
	Single	166	36.5%
	Married	170	37.4%
	Divorced	10	2.2%
	Widowed	4	0.9%
	Legally Separated	6	1.3%
	Unknown‡	99	21.8%
	Total	455	100.0%

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian

‡ Unknown includes unknown, unreported, and missing

Table 3.15 Antidepressant medication at index for individuals with an index event of an initial antidepressant prescription claim and meeting continuous clinic service eligibility criteria

Antidepressant medication	n	(%)
SSRI		
Sertraline	225	49.5%
Fluoxetine	59	13.0%
Escitalopram	61	13.4%
Paroxetine	30	6.6%
Citalopram	10	2.2%
SNRI		
Duloxetine	26	5.7%
Venlafaxine	15	3.3%
Atypical Antidepressants		
Bupropion	24	5.3%
Mirtazapine	5	1.1%
Total	455	100.0%

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor

Diagnostic descriptive statistics for subjects with an index event of an initial antidepressant prescription claim are presented in Table 3.16. A diagnosis of depression was present for 60.9% (n = 277) of patients with an index prescription for an antidepressant medication. The other psychiatric diagnoses most frequently associated with an index prescription claim for an antidepressant medication were anxiety disorders (19.3%, n = 88) and bipolar disorder (3.5%, n = 16).

Table 3.16 Depression and diabetes diagnostic status for subjects with an index event of an initial antidepressant prescription claim and meeting continuous clinic eligibility criteria.

Variable	n	(%)
Depresson diagnostic status		
Not present	178	39.1%
Present	277	60.9%
Total	455	100.0%
Diabetes diagnostic status		
Not present	346	76.0%
Present	109	24.0%
Total	455	100.0%

The analytic cohort for the hypotheses under Objective 3 was further restricted, as described in Chapter 2, to patients diagnosed with depression. This left 277 subjects eligible for inclusion in the final analytic cohort used to test hypotheses 3.1 to 3.8. Of these 277 subjects, 57 (20.6%) had a diagnosis of diabetes. Descriptive statistics for these 277 subjects with an index event of initial antidepressant prescription and a diagnostic status indicating the presence of depression are presented in Table. 3.17. The mean Charlson score was 1.39 (± 0.59) among subjects with a diagnosis of diabetes, and 0.16 (± 0.61) among those without a diagnosis of diabetes. Table 3.18 presents the frequency of type of antidepressant medication by diabetes status.

Table 3.17 Demographic characteristics for subjects with in index event of an initial antidepressant prescription claim and meeting continuous service eligibility criteria.

Variable	Diabetes present		Diabetes not present	
	n	(%)	n	(%)
Gender				
Female	43	75.4%	186	84.5%
Male	14	24.6%	34	15.5%
Total	57	100.0%	220	100.0%
Race/Ethnicity				
White (Hispanic)	42	73.7%	156	70.9%
White (non-Hispanic)	10	17.5%	48	21.8%
Black/African American	4	7.0%	9	4.1%
Other†	1	1.8%	2	0.9%
Unknown‡	0	0.0%	5	2.3%
Total	57	100.0%	220	100.0%
Marital Status				
Single	20	35.1%	81	36.8%
Married	14	24.6%	82	37.3%
Divorced	4	7.0%	2	0.9%
Widowed	0	0.0%	1	0.5%
Legally Separated	2	3.5%	1	0.5%
Unknown‡	17	29.8%	53	24.1%
Total	57	100.0%	220	100.0%
Behavioral health services status				
Not present	15	26.3%	88	40.0%
Present	42	73.7%	132	60.0%
Total	57	100.0%	220	100.0%

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian

‡ Unknown includes unknown, unreported, and missing

Table 3.18 Antidepressant medication at time of index for subjects with an index event of initial antidepressant prescription claim and meeting continuous clinic service eligibility criteria

Variable	Diabetes		Diabetes Not Present	
	n	(%)	n	(%)
SSRI				
Sertraline	32	56.1%	113	51.4%
Fluoxetine	14	24.6%	26	11.8%
Escitalopram	4	7.0%	28	12.7%
Paroxetine	0	0.0%	12	5.5%
Citalopram	2	3.5%	5	2.3%
SNRI				
Duloxetine	4	7.0%	8	3.6%
Venlafaxine	1	1.8%	9	4.1%
Atypical Antidepressants				
Bupropion	0	0.0%	17	7.7%
Mirtazapine	0	0.0%	2	0.9%
Total	57	100.0%	220	100.0%

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor

Hypothesis 3.1

H_0 3.1: There is no statistically significant relationship between diabetes diagnostic status and **type of initial antidepressant** (i.e., SSRI, non-SSRI) prescribed for patients with depression.

Testing of Hypothesis 3.1 was conducted via logistic regression with initial class of antidepressant medication as the dependent variable. The primary independent variable of interest in this analysis is diabetes diagnostic status, with covariate control for relevant variables as discussed in Chapter 2. The results of the logistic regression are summarized in Table 3.19.

SSRI medications were prescribed for 83.6 percent (n = 184) of patients without a diagnosis of diabetes, compared to 91.2 percent (n = 52) of subjects with a diagnosis of diabetes. After controlling for the influence of the included covariates, diabetes diagnostic status was associated with the initial class of antidepressant medication prescribed at a statistically significant level (B= -2.03, p = 0.002, OR 0.13, 95% CI 0.04 to 0.48). Based on the coding of the dependent variable with SSRI = 0 and non-SSRI = 1, this analysis indicates that subjects with a diagnosis of diabetes were less likely than their non-diabetic counterparts to receive initial treatment with a non-SSRI medication. Among the included covariates, only age was found to be associated with initial antidepressant class (B = 0.04, p = 0.046, OR 1.04, 95% CI 1.00 - 1.08). Each year increase in age was associated with a 4 percent increase in the odds of receiving a non-SSRI antidepressant as initial treatment. Based on these results, H_0 3.1 is rejected.

Table 3.19 Logistic regression of class of initial antidepressant medication on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, and behavioral health service status in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald	p-value	OR	95% CI	
Diabetes status	-2.03	0.67	9.28	**0.002**	0.13	0.04	0.48
Age	0.04	0.02	3.98	**0.046**	1.04	1.00	1.08
Male gender	0.61	0.47	1.67	0.196	1.84	0.73	4.61
White non-Hispanic	0.48	0.45	1.11	0.292	1.61	0.66	3.91
African-American	-0.16	0.84	0.04	0.847	0.85	0.16	4.44
Other race/ethnicity	0.50	1.04	0.23	0.633	1.64	0.21	12.62
Married	-1.13	0.63	3.24	0.072	0.32	0.09	1.11
Divorced, widowed, or other	0.78	0.42	3.48	0.062	2.18	0.96	4.94
Charlson score	0.52	0.28	3.40	0.065	1.68	0.97	2.93
Behavioral health service status	0.81	0.48	2.84	0.092	2.24	0.88	5.75
Constant	-4.25	0.98	18.77	**< 0.001**	0.01		

Dependent variable: initial antidepressant class: 0, SSRI; 1, non-SSRI.

Model $\chi^2 = 43.881$, df = 10, $p < 0.001$

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Hypothesis 3.2

H_0 3.2: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant switch status** in patients with depression.

Testing of Hypothesis 3.2 was conducted via logistic regression with antidepressant switch status as the dependent variable. The primary independent variable of interest in this analysis is diabetes diagnostic status, with covariate control for relevant variables as discussed in Chapter 2. The results of the logistic regression are summarized in Table 3.20.

A total of 45 patients in the cohort (n = 277) exhibited a switch in their antidepressant regimen based on the definitions described in Chapter 2. Patients with diabetes displayed an antidepressant switch in 10.4 percent (n = 6) of cases, while patients without a diagnosis of diabetes had an antidepressant switch in 17.7 percent (n = 39) of cases. After controlling for the influence of the covariates, there was no statistically significant association between diabetes status and antidepressant switch status (B = -0.082, p = 0.179, OR 0.44, 95% CI 0.13 - 1.45). Among the covariates, only reception of specialized behavioral health services was associated with antidepressant switch status (B = 0.96, p = 0.023, OR 2.61, 95% CI 1.14 - 5.98). Reception of behavioral health services was associated with a 2.61-fold increase in the odds of observing an antidepressant switch. Based on these results, these analyses failed to reject H_0 3.2.

Table 3.20 Logistic regression of antidepressant switch status on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald	p-value	OR	95% CI	
Diabetes status	-0.82	0.61	1.80	0.179	0.44	0.13	1.45
Age	< 0.01	0.02	0.07	0.798	1.00	0.96	1.03
Male gender	-0.02	0.45	0.00	0.962	0.98	0.40	2.37
White non-Hispanic	0.68	0.45	2.25	0.134	1.97	0.81	4.76
African-American	1.07	0.71	2.30	0.129	2.92	0.73	11.64
Other race/ethnicity	-0.26	1.12	0.06	0.813	0.77	0.09	6.90
Married	0.65	0.47	1.92	0.165	1.91	0.77	4.75
Divorced, widowed, or other	0.41	0.43	0.91	0.341	1.51	0.65	3.51
Charlson score	0.11	0.28	0.15	0.700	1.11	0.64	1.94
Behavioral health service status	0.96	0.42	5.17	**0.023**	2.61	1.14	5.98
Class of index AD medication	0.32	0.45	0.50	0.480	1.38	0.57	3.33
Constant	-2.67	11.16	11.16	**0.001**	0.07		

Dependent variable: Antidepressant switch status: 0, no switch; 1, switch.

Model $\chi^2 = 15.921$, df = 11, p = 0.144

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant.

Hypothesis 3.3

H_0 3.3: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant discontinuation status** in patients with depression.

Hypothesis 3.3 was evaluated via logistic regression with antidepressant discontinuation status as the dependent variable. The primary independent variable of interest in this analysis is diabetes diagnostic status, with covariate control for relevant variables as discussed in Chapter 2. The results of the logistic regression are summarized in Table 3.21.

A total of 197 subjects (71.1%) discontinued antidepressant treatment based on the definition of discontinuation as described in Chapter 2, with 71.9 percent of subjects with a diagnosis of diabetes (n = 41) and 70.9 percent of subjects without diabetes (n = 156) discontinuing initial antidepressant treatment. Diabetes diagnostic status was not associated with antidepressant discontinuation after controlling for the influence of the included covariates (B = 0.28, p = 0.542, OR 1.33, 95% CI 0.53 - 3.31). Among the covariates, only reception of behavioral health services was associated with a statistically significant relationship with antidepressant discontinuation status (B = -0.78, p = 0.016, OR 0.46, 95% CI 0.24 - 0.86). Reception of behavioral health services was associated with a 54 percent reduction in the odds of observing an antidepressant discontinuation among the subjects evaluated. Based on these analyses, H_0 3.3 was not rejected.

Table 3.21 Logistic regression of antidepressant discontinuation status on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald	p-value	OR	95% CI	
Diabetes status	0.28	0.47	0.37	0.542	1.33	0.53	3.31
Age	-0.01	0.01	0.68	0.410	0.99	0.96	1.02
Male gender	0.18	0.38	0.21	0.644	1.19	0.56	2.53
White non-Hispanic	-0.70	0.37	3.62	0.057	0.50	0.24	1.02
African-American	-0.74	0.62	1.42	0.233	0.48	0.14	1.61
Other race/ethnicity	0.12	0.86	0.02	0.885	1.13	0.21	6.06
Married	-0.01	0.36	0.00	0.988	0.99	0.49	2.01
Divorced, widowed, or other	0.15	0.34	0.20	0.654	1.17	0.59	2.29
Charlson score	-0.07	0.08	0.08	0.782	0.94	0.59	1.49
Behavioral health service status	-0.78	0.33	5.84	**0.016**	0.46	0.24	0.86
Class of index AD medication	0.10	0.40	0.06	0.802	1.11	0.50	2.43
Constant	1.98	0.63	10.04	**0.002**	7.25		

Dependent variable: Antidepressant discontinuation: 0, no discontinuation; 1, discontinuation.

Model $\chi^2 = 17.855$, df = 11, p = 0.085

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant.

Hypothesis 3.4

H_0 3.4: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant 6-month MPR.**

Hypothesis 3.4 was evaluated via implementation of the generalized linear model with 6-month medication possession ratio (MPR) as a continuous dependent variable. The primary independent variable of interest in this model was diabetes diagnostic status. The unadjusted mean 6-month MPR was 0.65 (± 0.28) for patients with a diagnosis of diabetes and 0.53 (± 0.30) for subjects without a diagnosis of diabetes.

The results of the multivariate analysis are presented in Table 3.22. After controlling for the influence of covariates, diabetes diagnostic status was not associated with 6-month MPR (B = 0.101, p = 0.088). Among the covariates, age (B = 0.004, p = 0.021) and behavioral health service status (B = 0.082, p = 0.033) were associated with 6-month MPR at a statistically significant level. Based on these analyses, each year increase in age was associated with an increase in the 6-month antidepressant MPR of 0.004 units. In addition, reception of behavioral health services was associated with a 0.082 unit increase in the 6-month MPR. None of the other covariates were associated with 6-month MPR. Based on the results of this model, H_0 3.4 was not rejected.

Table 3.22 Regression of 6-month medication possession ratio on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald Chi-Square	p-value
Intercept	0.339	0.076	20.04	**<0.001**
Diabetes status	0.101	0.059	2.92	0.088
Age	0.004	0.002	5.33	**0.021**
Male gender	-0.050	0.050	0.98	0.321
White non-Hispanic	0.018	0.049	0.14	0.713
African-American	-0.106	0.087	1.50	0.221
Other race/ethnicity	-0.153	0.107	2.03	0.154
Married	0.028	0.045	0.40	0.528
Divorced, widowed, or other	-0.070	0.044	2.52	0.113
Charlson score	0.001	0.030	< 0.01	0.986
Behavioral health service status	0.082	0.039	4.54	**0.033**
Class of index AD medication	-0.001	0.053	< 0.01	0.991

Dependent variable: 6-month medication possession ratio

Model $\chi^2 = 27.294$, df = 11, p = 0.004

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant.

Hypothesis 3.5

H_0 3.5: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **antidepressant 12-month MPR.**

Hypothesis 3.5 was evaluated via implementation of the generalized linear model with antidepressant 12-month MPR as the dependent variable. The primary independent variable of interest in this model was diabetes diagnostic status, with age, gender, race/ethnicity, marital status, Charlson score, behavioral health service status, and class of index antidepressant medication entered as covariates. The unadjusted mean 12-month MPR was 0.49 (± 0.32) for patients with a diagnosis of diabetes and 0.36 (± 0.29) for subjects without a diagnosis of diabetes.

The results of the multivariate analysis are presented in Table 3.23. After controlling for the influence of the included covariates, diabetes diagnostic status was associated with 12-month MPR at a statistically significant level (B = 0.130, p = 0.024). Among the covariates, only age was associated with 12-month MPR (B = 0.004, p = 0.011). Each year increase in age was associated with a 0.004 unit increase in the 12-month MPR. While behavioral health service status was not associated with 12-month MPR at the *a priori* alpha level of 0.05, there was a trend towards statistical significance observed for this variable (B = 0.074, p = 0.052). H_0 3.5 was rejected, based on the results of this analysis.

Table 3.23 Regression of 12-month medication possession ratio on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald Chi-Square	p-value
Intercept	0.157	0.074	4.46	**0.035**
Diabetes status	0.130	0.058	5.09	**0.024**
Age	0.004	0.002	6.40	**0.011**
Male gender	-0.052	0.049	1.14	0.285
White non-Hispanic	0.034	0.048	0.50	0.479
African-American	-0.108	0.085	1.62	0.203
Other race/ethnicity	-0.060	0.105	0.33	0.568
Married	0.021	0.044	0.23	0.628
Divorced, widowed, or other	-0.050	0.043	1.33	0.250
Charlson score	-0.018	0.030	0.35	0.553
Behavioral health service status	0.074	0.038	3.79	0.052
Class of index AD medication	< 0.001	0.052	< 0.01	0.997

Dependent variable: 12-month medication possession ratio.

Model $\chi^2 = 27.880$, df = 11, p = 0.003

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant.

Hypothesis 3.6

H_0 3.6: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status **and time to antidepressant non-persistence status.**

Hypothesis 3.6 evaluated time to antidepressant non-persistence using survival analysis methodology. As a preliminary evaluation of the bivariate association between diabetes diagnostic status and time to antidepressant non-persistence, Kaplan-Meier survival analysis was conducted. In this bivariate analysis, the median persistence time for patients with a diagnosis of diabetes was 90.0 days, compared to 60.0 days among patients without a diagnosis of diabetes. This difference was significant (log-rank p-value = 0.002).

Survival analysis was then performed using the Cox proportional hazards regression model. In this model, diabetes diagnostic status was the independent variable of interest and time to antidepressant non-persistence was the dependent variable. Age, gender, race/ethnicity, Charlson score, behavioral health services status, and class of initial antidepressant medication were entered as covariates. The results of this model are presented in Table 3.24. The graphical survival functions are presented in Figure 3.2. Based on this model, diabetes diagnostic status was not associated with time to non-persistence at a statistically significant level (B = -0.37, p = 0.094, HR 0.69, 95% CI 0.45 - 1.06). None of the covariates included in the model were associated with time to antidepressant non-persistence at a statistically significant level. On the basis of these results, H_0 3.6 was not rejected.

Table 3.24 Cox proportional hazards regression of time to antidepressant non-persistence on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald	p-value	HR	95% CI	
Diabetes status	-0.37	0.22	2.81	0.094	0.69	0.45	1.06
Age	-0.01	0.01	1.63	0.201	0.99	0.98	1.00
Male gender	0.09	0.18	0.24	0.626	1.09	0.77	1.55
White non-Hispanic	0.04	0.18	0.06	0.804	1.05	0.74	1.49
African-American	0.17	0.31	0.29	0.591	1.18	0.65	2.16
Other race/ethnicity	0.02	0.40	0.00	0.966	1.02	0.47	2.22
Married	0.04	0.16	0.06	0.811	1.04	0.76	1.43
Divorced, widowed, or other	0.21	0.16	1.69	0.193	1.24	0.90	1.71
Charlson score	< 0.01	0.12	0.00	0.988	1.00	0.80	1.25
Behavioral health service status	-0.18	0.14	1.76	0.184	0.83	0.64	1.09
Class of index AD medication	0.11	0.19	0.33	0.568	1.12	0.77	1.62

Dependent variable: time to antidepressant non-persistence.

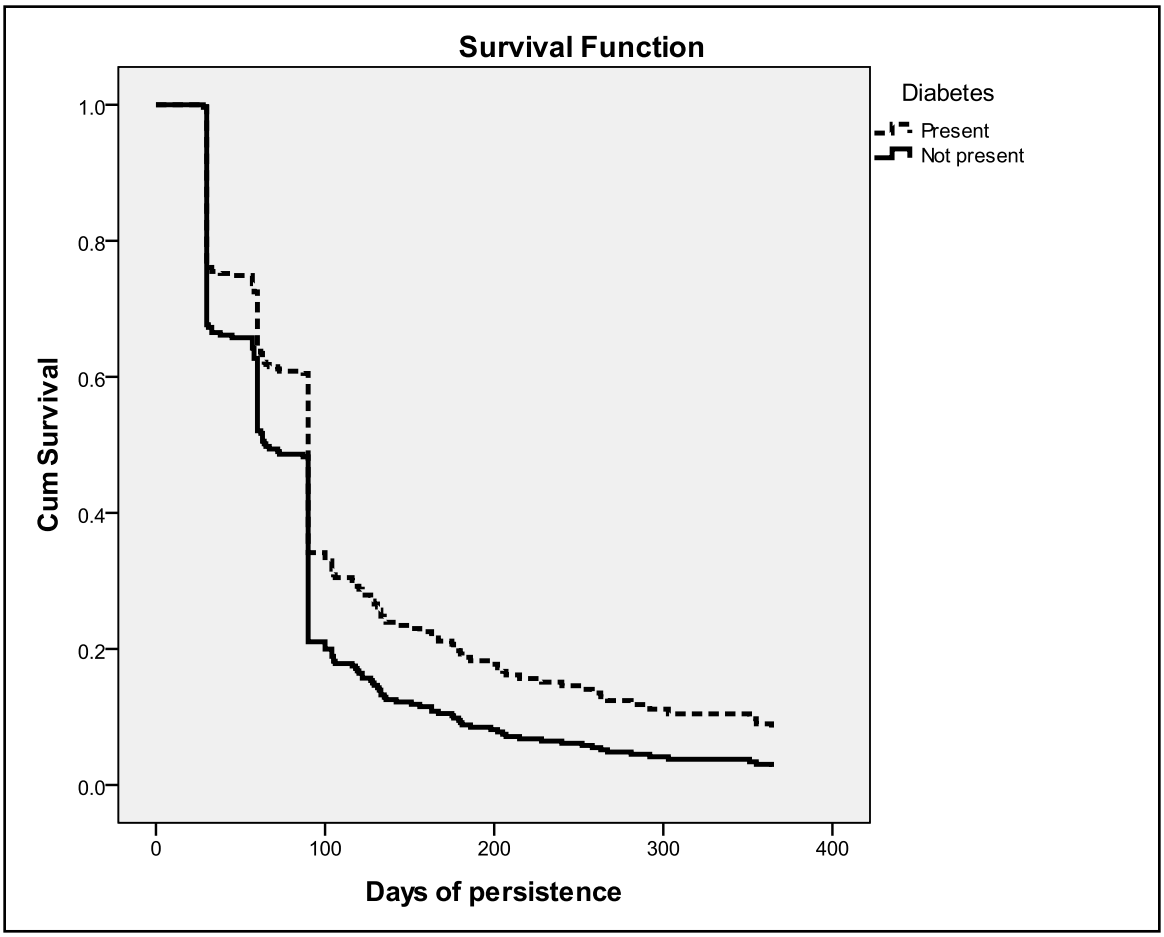
Model $\chi^2 = 14.547$, df = 11, p = 0.204

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant.

Figure 3.2 Survival function for Cox proportional hazards regression of time to antidepressant non-persistence on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression



Hypothesis 3.7

H_0 3.7: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **3-month antidepressant persistence status.**

The association between diabetes status and 3-month antidepressant persistence was evaluated via logistic regression with persistence status as the dependent variable and diabetes diagnostic status as the primary variable of interest. Covariates included in the model were age, gender, race/ethnicity, marital status, Charlson score, behavioral health service status, and initial antidepressant medication.

The unadjusted frequency of 3-month persistence with initial antidepressant treatment was 73.7 percent (n = 42) for subjects with a diagnosis of diabetes, and 44.5 percent (n = 98) for subjects without a diagnosis of diabetes. The results of the analyses related to Hypothesis 3.7 are presented in Table 3.25. After controlling for the influence of the included covariates, diabetes status was associated with a 3.83-fold increase in odds of antidepressant persistence at 3 months (B = 1.34, p = 0.004, OR 3.83, 95% CI 1.55 - 9.48). None of the covariates displayed a statistically significant association with 3-month persistence. H_0 3.7 was rejected on the basis of these results.

Table 3.25 Logistic regression of 3-month persistence status on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald	p-value	OR	95% CI	
Diabetes status	1.34	0.46	8.43	**0.004**	3.83	1.55	9.48
Age	0.02	0.01	1.98	0.160	1.02	0.99	1.04
Male gender	-0.18	0.37	0.24	0.622	0.84	0.41	1.71
White non-Hispanic	-0.07	0.36	0.04	0.851	0.93	0.46	1.89
African-American	0.37	0.66	0.31	0.576	1.44	0.40	5.22
Other race/ethnicity	-0.53	0.77	0.47	0.494	0.59	0.13	2.68
Married	0.15	0.32	0.21	0.650	1.16	0.61	2.19
Divorced, widowed, or other	-0.52	0.32	2.55	0.110	0.60	0.32	1.12
Charlson score	-0.13	0.24	0.29	0.591	0.88	0.55	1.40
Behavioral health service status	0.27	0.28	0.94	0.333	1.31	0.76	2.27
Class of index AD medication	-0.28	0.38	0.55	0.457	0.75	0.36	1.59
Constant	-0.90	0.55	2.66	0.103	0.41		

Dependent variable: 3-month antidepressant persistence: 0, non-persistent; 1, persistent.

Model $\chi^2 = 25.499$, df = 11, p = 0.008

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant.

Hypothesis 3.8

H_0 3.8: After controlling for appropriate covariates, there is no statistically significant relationship between diabetes diagnostic status and **12-month antidepressant persistence status.**

The purpose of Hypothesis 3.8 was to test the association between diabetes diagnostic status and 12-month antidepressant persistence (the dependent variable in this analysis). Covariates included in the logistic regression model were identical to those included in the analyses for Hypothesis 3.7.

The frequency of 12-month persistence was 7.0 percent (n = 4) for patients with a diagnosis of diabetes, and 2.3 percent (n = 5) for subjects without a diagnosis of diabetes. Results of the analysis related to Hypothesis 3.8 are presented in Table 3.26. After including the influence of the covariates into the model, diabetes diagnostic status was not associated with 12-month antidepressant persistence at a statistically significant level (B = 0.52, p = 0.663, OR 1.67, 95% CI 0.17 - 16.94). None of the covariates included in the model displayed a statistically significant association with 12-month antidepressant persistence. Based on these results, H_0 3.8 was not rejected.

Summary

The results of analyses related to hypotheses 3.1 through 3.8 are summarized in Table 3.26. Among the hypotheses related to Objective 3, hypotheses 3.1, 3.5, and 3.7 were rejected.

Table 3.26 Logistic regression of 12-month persistence status on diabetes diagnostic status, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, and initial class of antidepressant medication in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression

Variable	B	SE	Wald	p-value	OR	95% CI	
Diabetes status	0.52	1.18	0.19	0.663	1.67	0.17	16.94
Age	0.02	0.04	0.33	0.568	1.02	0.95	1.09
Male gender	0.15	0.94	0.02	0.874	1.16	0.19	7.26
White non-Hispanic	-0.03	0.87	0.01	0.972	0.97	0.17	5.38
African-American	-18.69	10885.58	< 0.01	0.999	< 0.01	NR	NR
Other race/ethnicity	-17.81	13811.02	< 0.01	0.999	< 0.01	NR	NR
Married	-1.52	1.70	1.70	0.192	0.22	0.02	2.15
Divorced, widowed, or other	-0.29	0.13	0.13	0.713	0.75	0.16	3.52
Charlson score	0.24	0.13	0.13	0.714	1.27	0.36	4.51
Behavioral health service status	1.40	1.61	1.61	0.205	4.06	0.46	35.51
Class of index AD medication	-0.75	0.41	0.41	0.519	0.47	0.05	4.59
Constant	-5.08	7.78	7.78	**0.005**	0.01		

Dependent variable: 12-month antidepressant persistence: 0, non-persistent; 1, persistent.

Model $\chi^2 = 10.510$, df = 11, p = 0.485

n = 277

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

AD, antidepressant; NR, not reported.

Table 3.27 Summary of hypothesis testing related to Objective 3

Hypothesis	Independent Variable		Dependent Variable		Statistical Test	Result
	Variable Name	Variable Type	Variable Name	Variable Type		
Objective 3. Evaluate the association between diabetes diagnostic status and antidepressant medication utilization patterns.						
H_0 3.1	Diabetes status	Dichotomous	AD class	Dichotomous	Logistic regression	Rejected
H_0 3.2	Diabetes status	Dichotomous	AD switch status	Dichotomous	Logistic regression	Failed to reject
H_0 3.3	Diabetes status	Dichotomous	AD discontinuation status	Dichotomous	Logistic regression	Failed to reject
H_0 3.4	Diabetes status	Dichotomous	6-month AD MPR	Continuous	Linear regression	Failed to reject
H_0 3.5	Diabetes status	Dichotomous	12-month AD MPR	Continuous	Linear regression	Rejected
H_0 3.6	Diabetes status	Dichotomous	Time to AD non-persistence	Continuous	Cox proportional hazards survival analysis	Failed to reject
H_0 3.7	Diabetes status	Dichotomous	3-month AD persistence	Dichotomous	Logistic regression	Rejected
H_0 3.8	Diabetes status	Dichotomous	12-month AD persistence	Dichotomous	Logistic regression	Failed to reject

AD, antidepressant; DM, diabetes mellitus; MPR, medication possession ratio

Covariates for H_0 3.1: age, gender, ethnicity, marital status, Charlson score, behavioral health services status.

Covariates for H_0 3.2 through 3.8 : covariates for H0 3.1 model + initial antidepressant class.

OBJECTIVE 4

Purpose

The purpose of Objective 4 is to evaluate the association between class of initial antidepressant medication treatment and antidepressant medication-taking behaviors in patients with diabetes. There were seven formal hypotheses tested in relation to Objective 4.

Cohort Description

Based on these procedures as detailed previously in Chapter 2, the analytic cohort for this objective included 109 subjects with a diagnosis of diabetes. Of these 109 subjects, 57 subjects were found to have a diagnosis of depression while 52 subjects did not have a diagnosis of depression in the medical record. For all of the subsequent analyses under Objective 4, the primary independent variable of interest (initial antidepressant class) was coded as SSRI = 0, non-SSRI = 1. Of the 109 subjects included in this cohort, there were a total of 93 subjects initiated on an SSRI antidepressant medication and 16 subjects initiated on a non-SSRI. Among the 16 subjects initiated on a non-SSRI medication, 11 were initiated on a serotonin norepinephrine reuptake inhibitor and 5 were initiated on bupropion. Clinical and demographic characteristics for the 109 subjects included in the analysis related to Objective 4 are presented in Table 3.28.

Fifty-two subjects (55.9%) in the SSRI group and 5 subjects (31.3%) in the non-SSRI group had a recorded diagnosis of depression. Fourteen (15.1%) and two (2.2%) of the subjects in the SSRI group, and two (12.5%) and one (6.3%) of the subjects in the non-SSRI group had diagnoses of anxiety disorders and bipolar disorder, respectively. Among patients initiated on SSRI treatment, 42 (45.2%) received specialized behavioral

health services while 6 (37.5%) initiated on non-SSRI treatment received these clinical services. The mean Charlson score was 1.45 (± 0.70) among patients initiated on SSRI medications, and 1.31 (± 0.48) for subjects initiated on other antidepressant medications. The mean number of diabetic complications was low in both groups (SSRI 0.41 ± 0.63; non-SSRI: 0.38 ± 0.62)

Table 3.28 Demographic and clinical characteristics by initial antidepressant medication class for subjects with an index event of an initial antidepressant prescription and a diagnosis of diabetes

Variable	SSRI		non-SSRI	
	n	(%)	n	(%)
Gender				
Female	71	76.3%	9	56.3%
Male	22	23.7%	7	43.8%
Total	93	100.0%	16	100.0%
Race/Ethnicity				
White (Hispanic)	73	78.5%	5	31.3%
White (non-Hispanic)	9	9.7%	4	25.0%
Black/African American	8	8.6%	5	31.3%
Other†	1	1.1%	2	12.5%
Unknown‡	2	2.2%	0	0.0%
Total	93	100.0%	16	100.0%
Marital Status				
Single	30	32.3%	6	37.5%
Married	36	38.7%	4	25.0%
Divorced	3	3.2%	1	6.3%
Widowed	1	1.1%	0	0.0%
Legally Separated	3	3.2%	0	0.0%
Unknown‡	20	21.5%	5	31.3%
Total	93	100.0%	16	100.0%
Behavioral health services status				
Not present	51	54.8%	10	62.5%
Present	42	45.2%	6	37.5%
Total	93	100.0%	16	100.0%

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian

‡ Unknown includes unknown, unreported, and missing

Hypothesis 4.1

H_0 4.1: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **antidepressant switch status** after controlling for appropriate covariates.

The purpose of Hypothesis 4.1 is to evaluate the association between initial class of antidepressant medication and antidepressant switch status among patients with diabetes. The hypothesis was tested via logistic regression of antidepressant switch status on class of initial antidepressant treatment. Covariates included in the model were age, gender, ethnicity, Charlson score, number of diabetic complications, behavioral health services status, and an indicator for treatment indication other than depression (coded such that diagnosis of depression = 0; no diagnosis of depression observed = 1).

The raw frequency of subjects who were classified as undergoing an antidepressant switch was 9.7 percent (n=9) for subjects initiated on an SSRI medication and 12.5 percent (n=2) for subjects initiated on a non-SSRI medication. The results of the multivariate logistic regression of switch status on initial class of antidepressant are presented in Table 3.29. After controlling for the covariates, there was no statistically significant relationship observed between initial antidepressant treatment and antidepressant switch during the follow-up period (B = -0.50, p = 0.638, OR 0.61, 95% CI 0.08 - 4.81). The only covariate which demonstrated a statistically significant association with antidepressant switch status was number of diabetic complications (B = 1.48, p = 0.042, OR 4.40, 95% CI 1.05 - 18.40). Each unit increase in the number of diabetic complications was associated with a 4.40-fold increase in odds of observing an antidepressant switch. Based on the results of this analysis, H_0 4.1 was not rejected.

Table 3.29 Logistic regression of antidepressant switch status on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald	p-value	OR	95% CI	
non-SSRI medication	-0.50	1.05	0.22	0.638	0.61	0.08	4.81
Age	0.02	0.04	0.37	0.540	1.02	0.95	1.11
Male gender	0.55	0.74	0.55	0.458	1.73	0.41	7.30
Race/ethnicity other than White Hispanic	1.04	0.84	1.53	0.216	2.83	0.54	14.79
Married	1.48	1.08	1.89	0.169	4.40	0.53	36.27
Divorced, widowed, or other	0.90	1.01	0.80	0.370	2.47	0.34	17.76
Charlson score	-1.33	0.93	2.02	0.155	0.26	0.04	1.65
No. diabetic complications	1.48	0.73	4.12	**0.042**	4.40	1.05	18.40
Behavioral health service status	1.26	1.25	1.01	0.316	3.51	0.30	40.90
Diagnosis other than depression	0.55	1.22	0.20	0.655	1.73	0.16	19.03
Constant	-4.58	2.52	3.30	0.069	0.01		

Dependent variable: Antidepressant switch status: 0, no switch; 1, switch.

Model $\chi^2 = 10.769$, df = 10, p = 0.376

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Hypothesis 4.2

H_0 4.2: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **antidepressant discontinuation status** after controlling for appropriate covariates.

The purpose of Hypothesis 4.2 is to evaluate the association between initial antidepressant medication class and antidepressant discontinuation status observed over one year of follow-up. As with the analysis of Hypothesis 4.1, the primary independent variable of interest was initial antidepressant medication class. Covariates included in the logistic regression model testing this hypothesis were identical to those included in the analysis of Hypothesis 4.1.

The discontinuation rate was 76.3 percent (n=71) among patients initiated on an SSRI and 75.0 percent (n = 12) among patients initiated on a non-SSRI medication. Results of the logistic regression model used to test Hypothesis 4.2 are presented in Table 3.30. There was no association observed between initial class of antidepressant medication and antidepressant discontinuation (B = 0.02, p = 0.983, OR 1.02, 95% CI 0.24 - 4.25). Among the covariates included in the model, only age was found to be associated with antidepressant discontinuation status (B = -0.05, p = 0.048, OR 0.95, 95% CI 0.90 - 1.00). Each year increase in age was associated with a 5 percent reduction in odds of antidepressant discontinuation. Based on the results of this analysis, H_0 4.2 was not rejected.

Table 3.30 Logistic regression of antidepressant discontinuation status on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald	p-value	OR	95% CI	
non-SSRI medication	0.02	0.73	0.00	0.983	1.02	0.24	4.25
Age	-0.05	0.03	3.90	**0.048**	0.95	0.90	1.00
Male gender	0.06	0.56	0.01	0.920	1.06	0.35	3.17
Race/ethnicity other than White Hispanic	-0.16	0.57	0.08	0.782	0.85	0.28	2.61
Married	0.47	0.61	0.59	0.441	1.60	0.48	5.35
Divorced, widowed, or other	0.22	0.58	0.15	0.702	1.25	0.40	3.85
Charlson score	0.19	0.49	0.15	0.702	1.20	0.46	3.13
No. diabetic complications	-0.11	0.52	0.04	0.838	0.90	0.33	2.47
Behavioral health service status	-0.25	0.62	0.17	0.683	0.78	0.23	2.62
Diagnosis other than depression	0.35	0.65	0.29	0.591	1.42	0.40	5.07
Constant	3.49	1.59	4.79	**0.029**	32.65		

Dependent variable: Antidepressant discontinuation status: 0, no discontinuation; 1, discontinuation.

Model $\chi^2 = 7.229$, df = 10, p = 0.704

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Hypothesis 4.3

H_0 4.3: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **6-month antidepressant MPR** after controlling for appropriate covariates.

The purpose of Hypothesis 4.3 is to evaluate the association between initial class of antidepressant medication treatment and 6-month antidepressant MPR. This hypothesis was tested via the generalized linear model with MPR treated as a continuous outcome variable. The primary independent variable of interest was class of initial antidepressant treatment. Covariates included in this model are identical to those utilized in the logistic regression models testing hypotheses 4.1 and 4.2.

The unadjusted mean 6-month MPR was 0.56 (± 0.29) for subjects initiated on an SSRI medication, and 0.57 (± 0.32) for those subjects initiated on a non-SSRI medication. The results of the regression model used to test Hypothesis 4.3 are presented in Table 3.31. There was no association observed between class of initial antidepressant treatment and 6-month MPR after controlling for the influence of covariates (B = 0.048, p = 0.549). None of the covariates included in the model were found to demonstrate a statistically significant association with 6-month MPR. Based on the results of this analysis, H_0 4.3 was not rejected.

Table 3.31 Regression of 6-month medication possession ratio on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald Chi-Square	p-value
Intercept	0.620	0.149	17.23	**<0.001**
non-SSRI medication	0.048	0.079	0.36	0.549
Age	0.001	0.003	0.03	0.871
Male gender	-0.068	0.062	1.21	0.271
Race/ethnicity other than White Hispanic	-0.002	0.065	0.00	0.978
Married	-0.034	0.066	0.26	0.608
Divorced, widowed, or other	0.087	0.066	1.76	0.185
Charlson score	-0.058	0.052	1.26	0.261
No. diabetic complications	0.055	0.055	0.98	0.323
Behavioral health service status	0.077	0.068	1.29	0.256
Diagnosis other than depression	-0.121	0.069	3.01	0.083

Dependent variable: 6-month medication possession ratio.

Model $\chi^2 = 21.222$, df = 10, p = 0.020

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Hypothesis 4.4

H_0 4.4: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **12-month antidepressant MPR** after controlling for appropriate covariates.

Hypothesis 4.4 tested the association between class of initial antidepressant medication and 12-month antidepressant MPR. The methodology utilized to test this hypothesis was identical to that used to test Hypothesis 4.3, with the exception that the dependent variable in this model was 12-month MPR, as opposed to 6-month MPR in the previous hypothesis.

The unadjusted mean 12-month MPR was 0.39 (± 0.30) for subjects initiated on an SSRI medication, and 0.42 (± 0.31) for those subjects initiated on a non-SSRI medication. The results of the regression model used to test Hypothesis 4.4 are presented in Table 3.32. There was no association demonstrated between class of initial antidepressant treatment and 12-month MPR, after controlling for the influence of the included covariates (B = 0.063, p = 0.440). Diagnosis other than depression was the only covariate that demonstrated a statistically significant association with 12-month MPR (B = -0.152, p = 0.034). The lack of an observed diagnosis of depression was associated with a 0.15 unit reduction in 12-month MPR. Based on these results, H_0 4.4 was not rejected.

Table 3.32 Regression of 12-month medication possession ratio on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald Chi-Square	p-value
Intercept	0.328	0.154	4.53	**0.033**
non-SSRI medication	0.063	0.082	0.60	0.440
Age	0.004	0.003	2.74	0.098
Male gender	-0.054	0.063	0.72	0.395
Race/ethnicity other than White Hispanic	-0.026	0.067	0.15	0.699
Married	-0.096	0.068	1.98	0.159
Divorced, widowed, or other	0.027	0.068	0.16	0.693
Charlson score	-0.058	0.053	1.19	0.276
No. diabetic complications	0.050	0.057	0.77	0.380
Behavioral health service status	0.053	0.070	0.58	0.445
Diagnosis other than depression	-0.152	0.072	4.51	**0.034**

Dependent variable: 12-month medication possession ratio.

Model $\chi^2 = 23.417$, df = 10, p = 0.009

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Hypothesis 4.5

H_0 4.5: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **time to antidepressant non-persistence status** after controlling for appropriate covariates.

Hypothesis 4.5 evaluated the association between initial class of antidepressant medication prescribed and time to antidepressant non-persistence. The relationship between initial antidepressant class and time to non-persistence was first evaluated in a bivariate manner, via Kaplan-Meier analysis. The median time to non-persistence with antidepressant treatment was 90 days for patients initiated on an SSRI medication and 55 days for patients initiated on a non-SSRI medication. This difference was not statistically significant with a log-rank p-value of 0.810.

After the preliminary bivariate association was evaluated, Cox proportional hazard regression was used to determine the relationship between class of initial antidepressant medication prescribed and time to antidepressant non-persistence after controlling for covariates. Covariates included in the model were age, gender, race/ethnicity, Charlson score, number of diabetic complications, behavioral health service status, and depression diagnostic status. The results of the model used to test Hypothesis 4.5 are presented in Table 3.33. The graphical survival function is presented in Figure 3.3 After controlling for the influence of the included covariates, there was no association observed between initial class of antidepressant and time to antidepressant non-persistence (B = 0.05, p = 0.877, HR 1.05, 95% CI 0.54 - 2.05). None of the included

covariates demonstrated a statistically significant association with time to antidepressant non-persistence. H_0 4.5 was not rejected based on the results of this analysis.

Table 3.33 Cox proportional hazards regression of time to antidepressant non-persistence on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald	p-value	HR	95% CI	
non-SSRI medication	0.05	0.34	0.02	0.877	1.05	0.54	2.05
Age	< 0.01	0.01	0.21	0.650	1.00	0.97	1.02
Male gender	0.01	0.26	0.00	0.982	1.01	0.60	1.67
Race/ethnicity other than White Hispanic	-0.02	0.27	0.00	0.956	0.99	0.58	1.68
Married	0.24	0.26	0.86	0.353	1.28	0.76	2.14
Divorced, widowed, or other	-0.07	0.27	0.07	0.797	0.93	0.54	1.60
Charlson score	0.16	0.22	0.54	0.461	1.18	0.76	1.81
No. diabetic complications	-0.18	0.23	0.63	0.426	0.83	0.53	1.30
Behavioral health service status	-0.34	0.29	1.40	0.237	0.71	0.40	1.25
Diagnosis other than depression	0.21	0.28	0.54	0.462	1.23	0.71	2.13

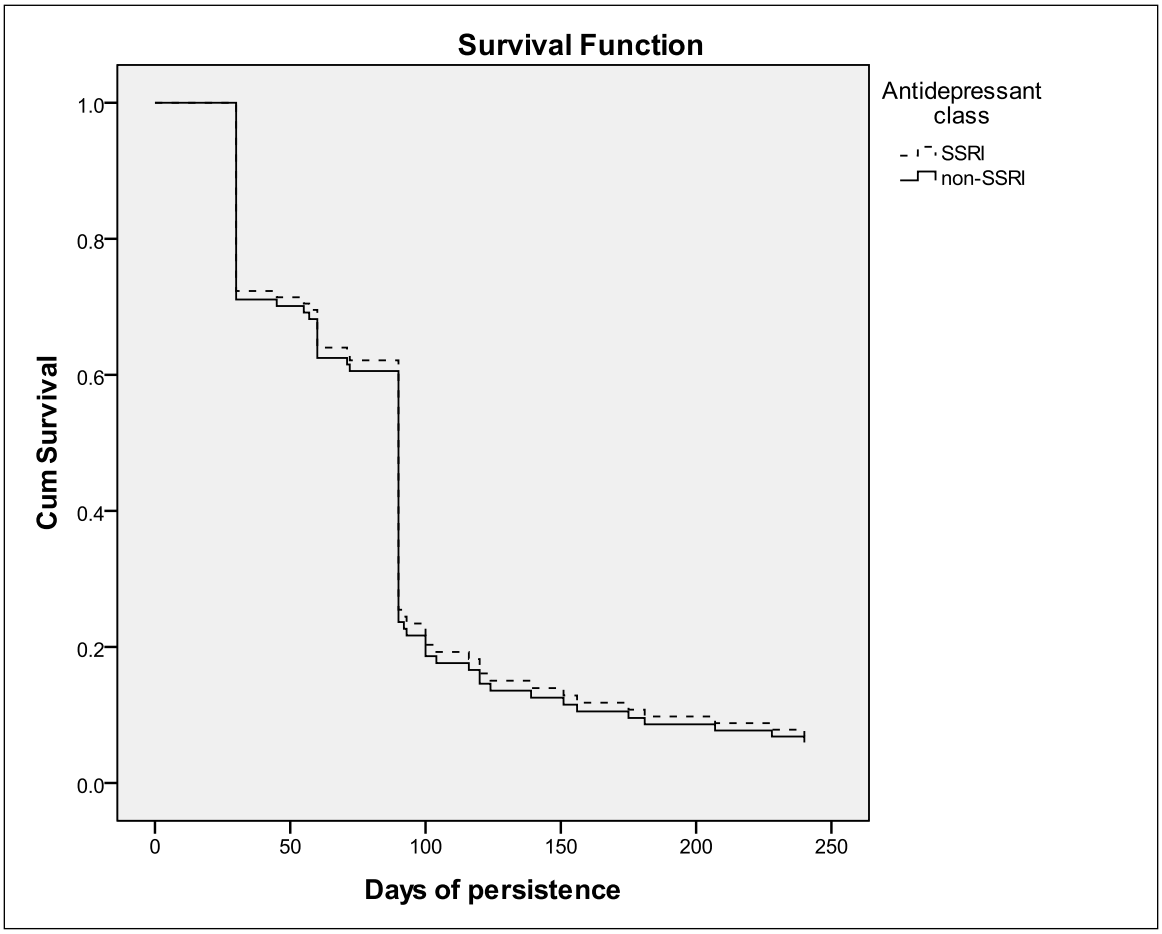
Dependent variable: time to antidepressant discontinuation

Model $\chi^2 = 9.448$, df = 10, p = 0.487

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Figure 3.3 Survival Function for Cox proportional hazards regression of time to antidepressant non-persistence on initial antidepressant class, age, gender, race/ethnicity classification, marital status classification, Charlson score, behavioral health service status, depression diagnostic status in a cohort of subjects with an index event of an initial antidepressant medication claim and a diagnosis of depression



Hypothesis 4.6

H_0 4.6: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **3-month antidepressant persistence status** after controlling for appropriate covariates.

The association between initial antidepressant medication and 3-month antidepressant persistence was evaluated via logistic regression. The dependent variable in this analysis was 3-month persistence evaluated as a dichotomous outcome variable with 3-month persistence coded as 1, and 3-month non-persistence coded as 0. The covariates included in this model are identical to the previous analyses under objective 4.

The 3-month persistence rate was 63.4 percent (n = 59) for subjects initiated on an SSRI medication, and 43.8 percent (n = 7) for subjects initiated on a non-SSRI medication. Results of the multivariate logistic regression of 3-month persistence status on class of index antidepressant medication are presented in Table 3.34. After controlling for covariates, there was no statistically significant association between class of initial antidepressant medication and 3-month persistence with antidepressant treatment (B = -0.84, p = 0.191, OR 0.43, 95% CI 0.12 - 1.52). There was no statistically significant relationship between any of the included covariates and 3-month antidepressant persistence. Based on the results of this analysis, H_0 4.6 was not rejected.

Table 3.34 Logistic regression of 3-month antidepressant persistence status on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald	p-value	OR	95% CI	
non-SSRI medication	-0.84	0.64	1.71	0.191	0.43	0.12	1.52
Age	-0.01	0.02	0.17	0.684	0.99	0.95	1.03
Male gender	0.05	0.50	0.01	0.928	1.05	0.39	2.81
Race/ethnicity other than White Hispanic	0.43	0.55	0.63	0.428	1.54	0.53	4.53
Married	0.22	0.54	0.17	0.680	1.25	0.43	3.60
Divorced, widowed, or other	0.23	0.55	0.17	0.679	1.25	0.43	3.65
Charlson score	-0.38	0.41	0.84	0.359	0.68	0.30	1.54
No. diabetic complications	0.15	0.45	0.12	0.732	1.17	0.48	2.81
Behavioral health service status	0.14	0.56	0.07	0.795	1.16	0.39	3.45
Diagnosis other than depression	-1.02	0.56	3.31	0.069	0.36	0.12	1.08
Constant	1.65	1.27	1.70	0.192	5.23		

Dependent variable: 3-month antidepressant persistence: 0, non-persistent; 1, persistent

Model $\chi^2 = 11.786$, df = 10, p = 0.300

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

Hypothesis 4.7

H_0 4.7: Among subjects with diabetes, there is no statistically significant relationship between type of initial antidepressant medication treatment and **12-month antidepressant persistence status** after controlling for appropriate covariates.

The association between initial antidepressant medication and 12-month persistence was evaluated via logistic regression. The dependent variable in this analysis was 12-month persistence evaluated as a dichotomous outcome variable. The covariates included in this model are identical to the previous analyses under Objective 4.

The 12-month persistence rate was 4.3 percent (n = 4) for subjects initiating on SSRI treatment and 12.5 percent (n = 2) for subjects initiating on a non-SSRI antidepressant treatment. Results of the multivariate logistic regression of 12-month persistence status on class of index antidepressant medication are presented in Table 3.35. There was no statistically significant association between class of initial antidepressant medication and 12-month persistence with antidepressant treatment after controlling for covariates (B = 0.03, p = 0.594, OR 1.03, 95% CI 0.92 - 1.16). Among the covariates, the only statistically significant association observed was for number of diabetic complications (B = 2.62, p = 0.014, OR 13.71, 95% CI 1.71 - 109.85). Each unit increase in the number of observed diabetic complications was associated with a 13.71-fold increase in the odds of 12-month antidepressant persistence. Based on the results of this analysis, H_0 4.7 was not rejected.

Summary

The results of analyses related to Objective 4 are summarized in Table 3.36. None of the null hypotheses tested under Objective 4 were rejected.

Table 3.35 Logistic regression of 12-month antidepressant persistence status on class of initial antidepressant medication, age, gender, race/ethnicity classification, marital status classification, Charlson score, number of diabetic complications, behavioral health service status, and depression status in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald	p-value	OR	95% CI	
non-SSRI medication	0.03	0.06	0.28	0.594	1.03	0.92	1.16
Age	-0.14	1.45	0.01	0.923	0.87	0.05	14.79
Male gender	-0.40	1.27	0.10	0.753	0.67	0.06	8.04
Race/ethnicity other than White Hispanic	-18.90	5827.44	<0.01	0.997	<0.01	NR	NR
Married	-0.45	1.09	0.17	0.683	0.64	0.08	5.46
Divorced, widowed, or other	-2.14	1.43	2.24	0.134	0.12	0.01	1.93
Charlson score	0.98	1.38	0.50	0.478	2.66	0.18	40.02
No. diabetic complications	2.62	1.06	6.08	**0.014**	13.71	1.71	109.85
Behavioral health service status	0.91	1.40	0.42	0.516	2.48	0.16	38.49
Diagnosis other than depression	0.26	1.46	0.03	0.857	1.30	0.07	22.66
Constant	-3.01	3.64	0.68	0.409	0.05		

Dependent variable: 12-month antidepressant persistence: 0, non-persistent; 1, persistent

Model $\chi^2 = 15.422$, df = 10, p = 0.117

n = 109

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

NR, not reported.

Table 3.36 Summary of hypothesis testing related to Objective 4

Hypothesis	Independent Variable		Dependent Variable		Statistical Test	Result
	Variable Name	Variable Type	Variable Name	Variable Type		
Objective 5. Evaluate the association between class of initial antidepressant medication treatment and antidepressant medication-taking behaviors in patients with type 2 diabetes and comorbid depression.						
H_0 4.1	AD class	Dichotomous	AD switch status	Dichotomous	Logistic regression	Failed to reject
H_0 4.2	AD class	Dichotomous	AD discontinuation status	Dichotomous	Logistic regression	Failed to reject
H_0 4.3	AD class	Dichotomous	6-month AD MPR	Continuous	Linear regression	Failed to reject
H_0 4.4	AD class	Dichotomous	12-month AD MPR	Continuous	Linear regression	Failed to reject
H_0 4.5	AD class	Dichotomous	Time to AD non-persistence	Continuous	Cox proportional hazards survival analysis	Failed to reject
H_0 4.6	AD class	Dichotomous	3-month AD persistence status	Dichotomous	Logistic regression	Failed to reject
H_0 4.7	AD class	Dichotomous	12-month AD persistence status	Dichotomous	Logistic regression	Failed to reject

AD, antidepresant; MPR, medication possession ratio.
Covariates for H_0 4.1 - 4.7: age, gender, ethnicity, marital status, diabetes diagnostic status, number of diabetic complications, Charlson score, behavioral health services status.

OBJECTIVE 5

The purpose of Objective 5 is to evaluate the relationship between antidepressant adherence and glycemic control, as measured by HbA1c value. There were two formal hypotheses tested under Objective 5.

Cohort Description

The analytic cohort for this objective consisted of subjects with an index antidepressant prescription and available HbA1c lab values during the follow-up period. There were a total of 106 subjects who met these criteria and were included in these analyses. Demographic characteristics for these subjects are presented in Table 3.37. The mean age of subjects included in these analyses was 49.88 (±9.60) years. Mean follow-up HbA1c value was 7.41 (± 1.74), and the mean Charlson score was 1.16 (±0.73). Eighty-three percent (n = 88) of subjects were treated with SSRI medications. Overall, sertraline was the most frequently observed antidepressant medication (50.0%), followed by fluoxetine (15.1%), escitalopram (11.3%), duloxetine (7.5%), bupropion (7.5%), paroxetine (5.7%) venlafaxine (1.9%) and citalopram (0.9%). The distribution of time in days between index antidepressant prescription claim and date of HbA1c observation is presented in Figure 3.4.

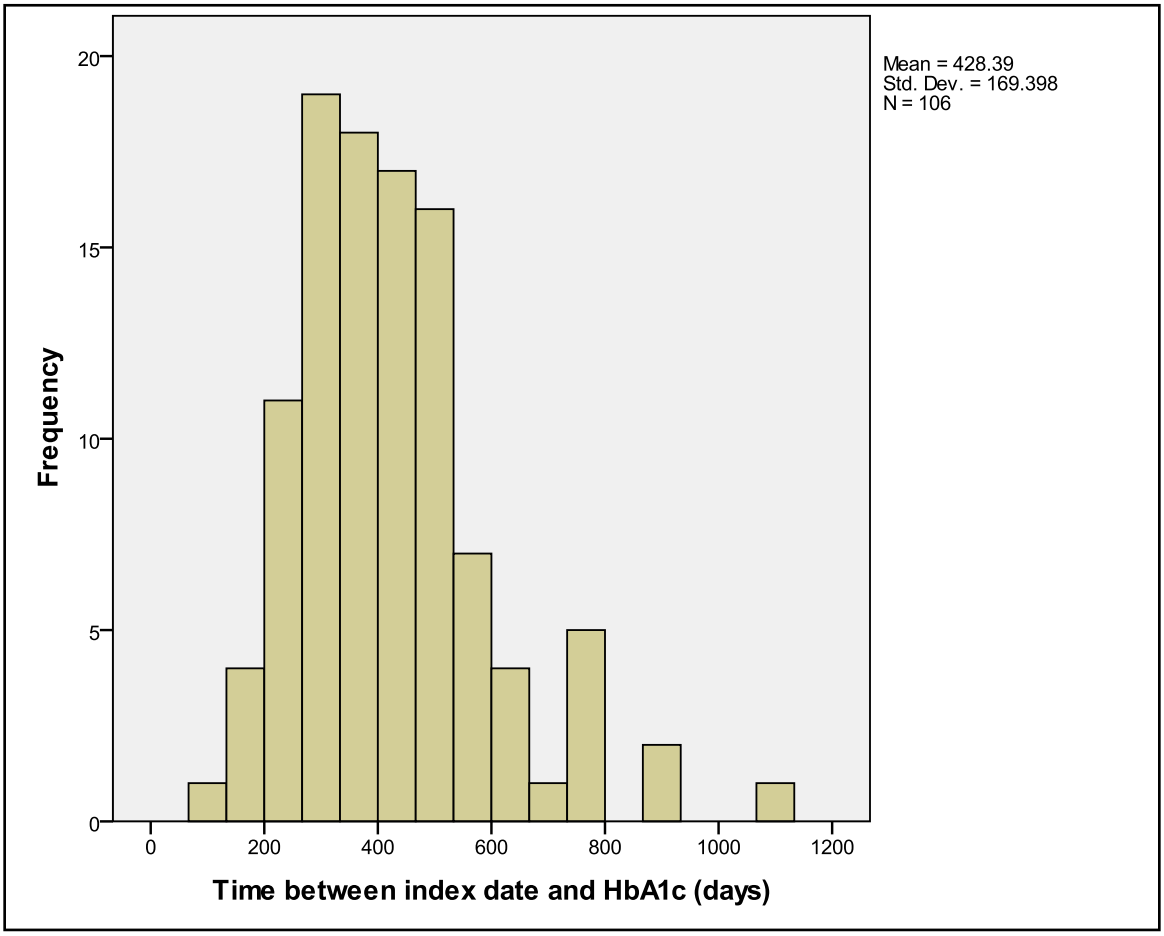
Table 3.37 Demographic characteristic for subjects with an HbA1c test during the follow-up period and an index event of an initial antidepressant prescription claim

Variable	n	(%)
Gender		
Female	85	80.2%
Male	21	19.8%
Total	106	100.0%
Race/Ethnicity		
White (Hispanic)	80	75.5%
White (non-Hispanic)	10	9.4%
Black/African American	12	11.3%
Other†	2	1.9%
Unknown‡	2	1.9%
Total	106	100.0%
Marital Status		
Single	37	34.9%
Married	39	36.8%
Divorced	4	3.8%
Widowed	1	0.9%
Legally Separated	2	1.9%
Unknown‡	23	21.7%
Total	106	100.0%

† Other includes American Indian/Alaskan native, Asian, Pacific Islander (not Hawaiian), Native Hawaiian, and Asian

‡ Unknown includes unknown, unreported, and missing

Figure 3.4 Distribution of time in days between index antidepressant prescription claim and hemoglobin A1c observation



Hypothesis 5.1

H_0 5.1: After controlling for appropriate covariates, there is no statistically significant relationship between **6-month antidepressant medication MPR** and follow-up HbA1c.

The association between 6-month antidepressant MPR and HbA1c value during follow-up was evaluated via the generalized linear model with HbA1c incorporated as a continuous outcome variable. The primary variable of interest was 6-month MPR. Covariates included in this analysis were age, gender, ethnicity, marital status, behavioral health services status, and Charlson comorbidity score.

The mean 6-month MPR was 0.57 (± 0.29). The Pearson correlation between 6-month MPR and HbA1c was $r = 0.22$ with a p-value of 0.018. Results of the statistical model testing Hypothesis 5.1 are presented in Table 3.38. After controlling for the influence of covariates, a statistically significant association was observed for 6-month antidepressant medication MPR and follow-up HbA1c (B = 1.69, p = 0.004). A 0.10 unit (10 percentage point) increase in 6-month MPR was associated with a 0.17 unit increase in HbA1c level. Age was the only covariate associated with post-index HbA1c (B = -0.03, p = 0.043), indicating that each year increase in age was associated with a 0.03 unit reduction in HbA1c value. Hypothesis 5.1 was rejected based on these results.

Table 3.38 Linear regression of post-index hemoglobin A1c value on 6-month antidepressant medication possession ratio, age, gender, race/ethnicity classification, marital status classification, behavioral health services status, and Charlson score in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald Chi-Square	p-value
Intercept	7.89	0.96	67.68	**<0.001**
6-month MPR	1.69	0.59	8.25	**0.004**
Age	-0.03	0.02	4.08	**0.043**
Male gender	-0.25	0.42	0.35	0.556
White non-Hispanic	-0.66	0.57	1.35	0.245
African-American	-0.01	0.53	0.00	0.989
Other race/ethnicity	-0.52	0.85	0.38	0.540
Married	0.32	0.40	0.63	0.427
Divorced, widowed, or other	0.06	0.40	0.02	0.875
Behavioral health service status	-0.34	0.33	1.03	0.309
Charlson score	0.37	0.22	2.71	0.100

Dependent variable: post-index HbA1c.

Model $\chi^2 = 16.649$, df = 10, p = 0.082

n = 106

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

MPR, medication possession ratio

Hypothesis 5.2

H_0 5.2: After controlling for appropriate covariates, there is no statistically significant relationship between **12-month antidepressant medication MPR** and follow-up HbA1c.

The association between 12-month antidepressant MPR and HbA1c value during follow-up was evaluated. The methodology utilized to test this hypothesis was identical to that used for Hypothesis 5.1, with the only exception being that the primary independent variable of interest for Hypothesis 5.2 was 12-month antidepressant MPR. Covariates included in this analysis were age, gender, ethnicity, marital status, behavioral health services status, and Charlson comorbidity score.

The mean 12-month antidepressant MPR was 0.39 (± 0.30). The Pearson correlation between 12-month MPR and HbA1c was r = 0.22 and was statistically significant (p = 0.026). Results of the statistical model testing Hypothesis 5.2 are presented in Table 3.39. After controlling for the influence of the included covariates, a statistically significant association was observed between 12-month antidepressant medication MPR and follow-up HbA1c (B = 1.61, p = 0.005). For every 0.10 unit (10 percentage point) increase in 12-month MPR, HbA1c was increased by 0.16 in the regression model. Age was the only covariate with a statistically significant association with HbA1c (B = -0.04, p = 0.015), indicating that each year increase in age was associated with a 0.04 unit reduction of HbA1c. Hypothesis 5.2 was rejected based on these results.

Summary

The results of hypothesis testing associated with Objective 5 are presented in Table 3.40. Both hypotheses 5.1 and 5.2 were rejected based on the results previously described.

Table 3.39 Linear regression of post-index hemoglobin A1c value on 12-month antidepressant medication possession ratio, age, gender, race/ethnicity classification, marital status classification, behavioral health service status, and Charlson score in a cohort of diabetic subjects with an index event of an initial antidepressant medication claim

Variable	B	SE	Wald Chi-Square	p-value
Intercept	8.49	0.89	90.52	**<0.001**
12-month MPR	1.61	0.57	8.04	**0.005**
Age	-0.04	0.02	5.86	**0.015**
Male gender	-0.21	0.42	0.25	0.616
White non-Hispanic	-0.62	0.57	1.18	0.278
African-American	-0.02	0.53	0.00	0.963
Other race/ethnicity	-0.15	0.84	0.03	0.856
Married	0.39	0.40	0.92	0.337
Divorced, widowed, or other	0.11	0.40	0.08	0.782
Behavioral health service status	-0.27	0.33	0.70	0.403
Charlson score	0.33	0.22	2.22	0.136

Dependent variable: post-index HbA1c.

Model $\chi^2 = 16.459$, df = 10, p = 0.087

n = 106

Comparison group for race/ethnicity classification is White Hispanic; comparison group for marital status classification is Single.

MPR, medication possession ratio

Table 3.40 Summary of hypothesis testing related to Objective 5

Hypothesis	Independent Variable		Dependent Variable		Statistical Test	Result
	Variable Name	Variable Type	Variable Name	Variable Type		
Objective 5. Evaluate the relationship between antidepressant medication adherence and glycemic control.						
H_0 5.1	6-month AD MPR	Continuous	HbA1c	Continuous	Linear regression	Rejected
H_0 5.2	12-month AD MPR	Continuous	HbA1c	Continuous	Linear regression	Rejected

DM, diabetes mellitus, MPR, medication possession ratio.

Covariates for H_0 5.1-5.2: age, gender, ethnicity, martial status, behavioral health service status, Charlson score.

Chapter 4: Discussion

OVERVIEW

The purpose of this chapter is to discuss the results and implications of this study. The study goals are briefly summarized in the following section, followed by a discussion of the results for each of the objectives and their related hypotheses.

STUDY GOALS

The overall goal of this study was to evaluate the relationships between diabetes and depression, with a specific focus on epidemiology and antidepressant medication-taking behaviors. There were 5 primary aims of this study:

1) To evaluate diabetes as a risk factor for incident diagnosis of depression among a cohort of indigent care patients;
2) To determine the relationship between demographic and clinical factors and incident depression among diabetic patients;
3) To examine the association between diabetes and antidepressant medication utilization patterns among patients with depression;
4) To evaluate the association between class of initial antidepressant medication treatment and antidepressant medication-taking behaviors among patients with diabetes; and
5) To determine the relationship between antidepressant medication adherence and glycemic control in patients with diabetes.

OBJECTIVE 1: DIABETES AS A RISK-FACTOR FOR DEPRESSION

The purpose of Objective 1 was to evaluate the association between prevalent diabetes and incident diagnosis of depression among a group of indigent primary care patients. A total of 2,394 subjects without prevalent depression were identified. Subjects included in this analysis were primarily classified as female (71.8%) and White Hispanic (75.9%). In comparison, the total clinic population over the same timeframe (n = 34,152) was classified as 69.4 percent female and 67.3 percent White Hispanic.

The prevalence of diabetes during the 12-month screening period was 26.5 percent. The prevalence found in this study of indigent primary care patients is higher than the prevalence observed in the general population.[64,199,200] The 12-month incidence of diabetes during the follow-up period was 3.8 percent. The incidence of diabetes in this population is also higher than that observed in the general population.[201] Of note, a high proportion of subjects included in this study were classified as White Hispanic race/ethnicity, a known risk factor for diabetes.[65]

Estimates of the point prevalence of depression vary by treatment setting, increasing as you move from the general population (2-4%) to the primary care setting(5-10%), to the inpatient setting (6-14%).[202] The prevalence of depression in the current study was 17.0 percent during the 12-month screening period. In comparison, the lifetime prevalence of depression in the general population has been estimated to be 16.2 percent.[26]

Over the entire 24-month observation period, the cross-sectional prevalence of depression among subjects with a diagnosis of diabetes was 20.0 percent. This compares to the overall prevalence of depression among diabetic patients estimated by Anderson et al. at 25.3 percent.[115] Of note, all of the studies included in the analysis conducted by Anderson et al. evaluated depression by either self-report rating scale or diagnostic

interview. The current study utilized ICD-9 CM diagnostic codes to identify diagnosis of depression.

The overall incidence of depression was 6.8 percent during the 12-month follow-up period, which is higher than the estimated incidence of depression from the Baltimore Epidemiological Catchment Area study (1.6%).[203] The 12-month incidence of depression was 5.2 percent for patients with a diagnosis of diabetes and 7.4 percent for patients without a prevalent diagnosis of diabetes. After controlling for relevant clinical and demographic factors, prevalent diabetes was found to have a negative association with a diagnosis of incident depression during 12 months of follow-up. The odds for a diagnosis of incident depression were 42 percent lower among subjects with a diagnosis of prevalent diabetes compared to those without a diagnosis of diabetes. Bivariate analysis, not controlling for covariate influence, displayed a trend towards a negative association between diabetes and incident depression ($p = 0.052$); however, the analysis did not result in a statistically significant association.

Exploratory cross-sectional bivariate correlations were evaluated to assess the correlation between diabetes and depression during the screening period, the follow-up period, and the overall observation timeframe. The purpose of these post-hoc exploratory analyses was to determine whether the relationship between incident depression and diabetes diagnostic status was an artifact related to rapid screening and identification of depression among patients with diabetes during the screening period. For each of these timeframes evaluated, the bivariate correlation between diagnosis of diabetes and depression was low, negative, and statistically significant. These exploratory analyses confirm that the relationship between prevalent diabetes and depression diagnostic status was consistently inverse across all timeframes evaluated, and whether depression was evaluated in terms of incident or prevalent cases.

In the multivariate regression model, greater age, female gender, and White non-Hispanic race/ethnicity were associated with increased odds of diagnosis of depression. These findings are similar to other research that has found these factors associated with risk for depression.[7,8] In the multivariate model evaluating depression diagnostic status, male gender was associated with a 40 percent decrease in odds of diagnosis of depression during follow-up (i.e., female gender was associated with a 1.6-fold increase in odds of an incident diagnosis of depression during follow-up). White non-Hispanic race/ethnicity was associated with 3.24-fold increased odds of diagnosis of depression compared to individuals classified as White Hispanic. This latter finding is presented within the context of previous research suggesting under-recognition and under-treatment of depression among Hispanic patients.[120,204-206] Of particular relevance, Shah and Huffman found that screening rates for depression among Hispanic patients with diabetes was extremely low despite a high prevalence of depression in this population.[120]

It is possible that factors related to treatment that were not measured in the current study may have affected the outcome. In a large, multiyear study evaluating the relationship between prevalent diabetes and incident depression, Golden et al. found that diabetic patients receiving treatment for diabetes had an increased risk of incident depression, but not untreated diabetic patients.[123] In addition, there was no relationship found between impaired fasting blood glucose status and an incident diagnosis of depression. Although in the study conducted by Golden et al. the estimates of risk attributable to prevalent diabetes did not achieve statistical significance, the point estimate for the odds of incident depression was < 1.0 for both untreated diabetes (OR 0.73, 95% CI 0.41-1.30) and impaired fasting blood glucose (OR 0.80, 95% CI 0.63-1.02). The current analyses did not incorporate diabetes treatment status as a covariate in the model. Research suggests that not only treatment status, but simple awareness of a

diagnosis of diabetes may increase the risk for depression[125]. Health beliefs, disease state knowledge, and insight may be important factors in terms of understanding the association between diabetes and depression, especially among indigent care patients.

A number of other factors may help explain the findings of the current study. Perhaps most noteworthy is that the cohort of subjects included in these analyses were drawn from a population of indigent care patients in a primary care setting. Individuals included in this cohort were primarily classified as White Hispanics, with relatively limited representation of White non-Hispanics and African-Americans. Previous research conducted by Zhang et al. found no increase in the prevalence of depression among Hispanic men and women diagnosed with diabetes .[117] Other research has found a higher prevalence of depression among Hispanics diagnosed with diabetes in a community sample and in a primary care setting.[118,119] These studies assessed depression and severity of depression by administration of validated rating scale instruments, while the current study utilized diagnostic coding in the electronic patient medical record. As mentioned previously, diagnosis and treatment of depression among minority patients in general, and Hispanics in particular, have been shown to be inadequate.[120,204-206] The use of diagnostic coding to identify depression, rather than direct clinical assessment may have resulted in an underestimate of the presence of depression in this patient population.

It is also possible that the period of follow-up was not sufficient to capture incident diagnoses of depression among patients with diabetes. Research that has found an association between diabetes and incident depression covered a significantly longer time-frame (3.1 years) than the current 12-month analysis.[123] However, other research using an even longer period of follow-up (4.5 years) did not find a relationship between diabetes and incident depression.[207] In addition, recent research published in August, 2010 suggests that new-onset depressive symptoms related to diabetes may not emerge

for a prolonged period of time, over a year, after diagnosis of diabetes.[208] The current timeframe was dictated by data availability. As future data becomes available from the data sources used for this study, it may be worthwhile to reevaluate the association between diabetes and incident depression using a longer follow-up period.

Another factor that may have influenced the results of these analyses is related to the continuous service criterion. In order to be included in the analytic cohort for this analysis, individuals were required to have 24 months of continuous service eligibility. Since eligibility determinations are tied to presentation at the clinic for services, there may be a systematic bias among patients with longer periods of service eligibility compared to those with shorter periods. Patients who are relatively healthy require fewer clinic services, present to the clinic less frequently, and thus are more likely to have significant lapses in continuous service eligibility. Patients with chronic medical conditions, on the other hand, may present to the clinic more frequently for medical care and may be more likely to establish a sufficient period of continuous service eligibility.

The continuous service criterion utilized for this study may have resulted in patients with more chronic and severe medication conditions such as asthma, cardiovascular disease, and other chronic medical conditions being included in the analytic cohort with a high frequency. Many of these chronic medical conditions have been associated with increased risk for mood disorders.[209,210] While this study attempted to control for the influence of medical comorbidity via inclusion of the Charlson score as a covariate, a number of conditions with a relatively well established association with increased risk for depression are not captured by the Charlson score (e.g., hepatitis C infection). It is possible that the presence of such medical conditions associated with depression among non-diabetic subjects included in these analyses may have biased the study results.

Summary

The unadjusted 12-month incidence of depression among diabetes patients was 5.2 percent for patients with a diagnosis of diabetes and 7.4 percent for patients without diabetes. Among this cohort of indigent care patients, after controlling for covariates, prevalent diabetes was associated with reduced odds of an incident diagnosis of depression during 12 months of follow-up. Greater age, female gender and White non-Hispanic ethnicity were associated with increased odds of incident depression, while marital status classification of divorced, widowed or other was associated with reduced odds of incident diabetes diagnostic status. Factors related to the demographic make-up of the cohort, the duration of study follow-up, and the continuous service eligibility requirement may have influenced the observed results.

OBJECTIVE 2: RISK FACTORS FOR A DIAGNOSIS OF DEPRESSION AMONG PATIENTS WITH DIABETES

The purpose of Objective 2 was to identify risk factors for a diagnosis of depression among patients with diabetes. A total of 179 subjects with diabetes were included in the logistic regression model. Age, gender, ethnicity, marital status, HbA1c level, number of diabetic complications, and Charlson score were evaluated for their association with incident diagnosis of diabetes.

In the multivariate analysis, none of the factors evaluated were associated with an incident diagnosis of depression at a statistically significant level. Among the factors evaluated, only age and African-American race achieved a p-value less than 0.10 ($p = 0.093$ and $p = 0.083$, respectively). In terms of directionality, the odds ratio for age was < 1.0, while the odds ratio for classification as African-American was > 1.0. While neither of these factors were associated with an incident diagnosis of depression at a statistically significant level, younger age has been associated with increased prevalence of depression among diabetic patients.[119,211-213] African-American race/ethnicity has likewise been associated with increased risk for depression among diabetic patients.[213] Previous research has linked obesity, smoking status, and educational level with increased risk of depression; however, these data were not available for inclusion in the current study. [212,213]

Of note, the sample size for this analysis was limited to 179 subjects with available HbA1c laboratory values during the screening period. The restriction of the sample size available for this analysis may have resulted in insufficient power to detect meaningful differences in odds of a diagnosis of incident depression. The pre-study power analysis assumed identification of a sample size of 1,000 subjects with diabetes for this analysis. The primary factors resulting in the small sample size available for these

analyses was the 24-month continuous service eligibility requirement and the lack of HbA1c data for the majority of subjects with a prevalence diagnosis of diabetes.

The analyses related to Objective 1 found that diabetes was inversely associated with incident diagnosis of depression. In the analysis related to Objective 2, a relatively small number of cases of incident depression during the 12-month follow-up were observed. Among the 179 subjects included in this analysis, only 7 (3.9%) displayed an incident diagnosis of depression during the 12-month follow-up period. Logistic regression is sensitive to the number of events observed relative to the number of variables included in the model. A low event observed/variables ratio may result in bias in the regression coefficients, large variance estimates, improper coverage of the confidence intervals, and paradoxical associations.[214] The low event rate likely adversely affected the stability and validity of the logistic model utilized for these analyses.

Post-hoc exploratory analyses were conducted evaluating risk factors for a diagnosis of prevalent depression in a cross-sectional manner over the entire 24-month study period. Individuals were classified as having a diagnosis of diabetes and/or depression if they demonstrated a diagnostic code for either disorder at any point over the 24-month timeframe. Depression diagnostic status was regressed on age, gender, ethnicity, marital status, and Charlson score for patients with a diagnosis of diabetes. HbA1c value was not incorporated in this exploratory analysis due to the impact on sample size. A total of 845 subjects with a diagnosis of diabetes were identified. Female gender and White non-Hispanic race/ethnicity classification were associated with increased odds of a prevalent diagnosis of depression. None of the other variables included in the exploratory analysis achieved statistical significance. Female gender and White non-Hispanic race/ethnicity were also found to be associated with increased odds of incident depression in the analyses related to Objective 1. These findings are

compatible with previous research that has found that the factors associated with increased risk for depression among diabetic patients are similar to the factors that increase risk for depression in the general population.[115] While this post-hoc analysis was only exploratory, and no definitive conclusions can be reached based on these data, these data may assist in the development of future research questions evaluating the epidemiological relationship between diabetes and depression.

Summary

No statistically significant association was observed between any of the demographic and clinical factors evaluated and incident depression diagnostic status. The restricted sample size and the low frequency of observed cases of incident depression during follow-up likely adversely affected the stability and validity of the *a priori* analysis. The results of exploratory analyses evaluating the association between demographic and clinical factors associated with a prevalent diagnosis of depression among subjects with diabetes may be useful to inform future research in this area. In these exploratory analyses, female gender and classification as White non-Hispanic were associated with increased odds of a prevalent diagnosis of depression.

OBJECTIVE 3: DIABETES AND ANTIDEPRESSANT MEDICATION-TAKING BEHAVIORS

The purpose of Objective 3 was to evaluate the association between diabetes diagnosis status and antidepressant medication-taking behaviors. Diagnosis of diabetes was found to be associated with increased odds of receiving an SSRI vs. a non-SSRI medication as initial antidepressant treatment. There was no association between diabetes diagnostic status and either antidepressant switch or discontinuation. Diagnosis of diabetes was associated with an increase in 12-month antidepressant medication adherence, but not 6-month adherence. Among the persistence outcomes evaluated, only 3-month persistence was associated with diabetes diagnostic status. Individuals with a diagnosis of diabetes were 3.83-fold more likely to be classified as persistent with initial antidepressant treatment at 3 months.

In this evaluation, diagnosis of diabetes was associated with increased likelihood of receiving an SSRI treatment as the initial medication treatment for depression. A number of studies have evaluated the acute phase efficacy of antidepressant treatment for depression in patients with diabetes.[157-162] One of these studies evaluated the use of nortriptyline,[157] and one evaluated the use of bupropion.[158] No controlled studies have evaluated the use of SNRI medications such as duloxetine and venlafaxine as an acute phase treatment for depression in diabetic patients. While these latter medications have demonstrated efficacy as treatment for diabetic complications such as peripheral neuropathy in patients without depression, there is a lack of research data to inform their use targeting core psychopathology associated with depression in this patient population.[215,216]

In this evaluation, the difference observed in terms of initial antidepressant prescribing patterns was driven by the "atypical antidepressants" bupropion and

mirtazapine. Among subjects without a diagnosis of diabetes, 8.5 percent of subjects were initiated on either bupropion (n = 17) or mirtazapine (n = 2), while among subjects with diabetes, there were no individuals initiated on these medications. The rate of SNRI treatment among patients without diabetes (7.7%) was similar to that among patients with diabetes (8.8%). The observed differences in initial antidepressant prescribing patterns among diabetic compared to non-diabetic patients may represent a number of clinical considerations including: the evidence base (or lack thereof) for specific agents in this setting, metabolic side effect profile associated with certain agents, efficacy for treatment of co-occurring conditions, cost considerations, or individual patient-level clinical considerations.

A total of 45 patients (16.2%) overall switched their antidepressant regimen over 12 months of observation. This rate is slightly higher than the switch rate measured in a demographically similar group of patients over a 3-month period (13%).[217] Patients with a diagnosis of diabetes switched antidepressant treatment in 10.4 percent of cases compared to 17.7 percent among patients without a diagnosis of diabetes. There was no statistically significant association observed between diabetes diagnostic status and antidepressant switch.

Overall, 71.1 percent (n = 197) of subjects discontinued antidepressant treatment within 12 months of initiation. The discontinuation rate in this study was much higher than the 3-month discontinuation rate observed by Bull et al. at 20 percent.[217] The higher discontinuation rate is likely due to the significantly longer period of follow-up in the current study. Among patients with diabetes, 71.9 percent discontinued antidepressant treatment, while 70.9 percent of subjects without a diagnosis of diabetes were observed to discontinue treatment. Again, there was no statistically significant association observed between diabetes diagnostic status and antidepressant discontinuation.

In the multivariate models, reception of behavioral health services was associated with both antidepressant switch and antidepressant discontinuation, although in different directions. Behavioral health services are add-on services provided to patients within the clinics on a referral basis. Physicians can refer patients for these services, which are provided by psychiatrists and clinical social workers and include interventions targeting specific behavioral health needs including medication management. Reception of these services was associated with a 2.61-fold increase in the odds of antidepressant medication switch. While no data were available to determine the clinical rationale for switching medications, this association may represent more active case and medication management for patients receiving these specialized services. Participation in the behavioral health program was also associated with a 54 percent reduction in odds of antidepressant discontinuation. Similar findings in other studies suggest that behavioral health interventions may be associated with decreased rate of discontinuation of antidepressant treatment.[217,218]

Medication adherence was evaluated in terms of the medication possession ratio calculated with a fixed interval denominator. Medication possession ratio during both a 6- and 12-month period after index was evaluated. After covariate control, diabetes diagnostic status was associated with a higher level of medication adherence at 12-months ($p = 0.024$), but the relationship did not achieve statistical significance at the 6-month evaluation ($p = 0.088$). Greater age was associated with increased medication adherence for both the 6-month and 12-month evaluations. Increased age has been associated with higher rates of psychotropic medication adherence in some studies, but not others.[219-221, 222] Behavioral health services status was associated with higher 6-month medication adherence. In the model evaluating 12-month medication adherence, behavioral health services status did not achieve statistical significant at the $p = 0.05$

level, but a trend towards statistical significance was observed ($p = 0.052$). As previously discussed, engaging with specialty behavioral health interventions may be associated with increased medication adherence. This effect may be mediated by enhanced medication education, coping strategy education, and more frequent clinical assessment and interaction for patients receiving these services.

Antidepressant medication persistence was evaluated in terms of time to antidepressant non-persistence as well as dichotomous persistence status at 3- and 12-month intervals. There was no relationship observed between diabetic diagnostic status and time to antidepressant non-persistence. Diagnosis of diabetes was associated with an increase in 3-month persistence (OR 3.83, $p = 0.004$), but not persistence at 12 months (OR 1.67, $p = 0.663$).

The persistence findings may be related to differences in physician prescribing patterns for patients with chronic medical conditions such as diabetes. In particular, a greater proportion of diabetic patients received a 90-day supply of their initial antidepressant medication fill than did patients without a diagnosis of diabetes. A total of 61.4 percent ($n = 35$) of subjects with a diagnosis of diabetes had an initial antidepressant prescription claim with a days supply ≥ 90 days, compared to 27.7 percent ($n = 61$) of subjects without a diagnosis of diabetes. The observation that the difference in 3-month persistence was not maintained at the 12-month interval suggests that the difference in level of persistence observed at 3 months was related to the observed differences in the initial days supply prescribed rather than differences in patient-level medication-taking behaviors.

Summary

A total of 277 subjects receiving antidepressant therapy and with an associated diagnosis of depression were included in objective 3 analyses. Subjects with a diagnosis of diabetes were more likely to receive an SSRI antidepressant medication as their initial treatment compared to a non-SSRI medication. This observation appeared to be related to a lower frequency of prescribing the atypical antidepressants bupropion and mirtazapine among diabetic patients. There was no association observed between diabetes diagnostic status and either antidepressant switch or antidepressant discontinuation. Diabetes diagnostic status was associated with a higher level of medication adherence at 12 months, but not at 6 months. There was no association between diabetes diagnostic status and time to non-persistence or 12-month antidepressant persistence. The association between diabetes diagnostic status and 3-month persistence appears to have been driven by differences in antidepressant prescribing patterns, specifically the initial days supply of medication prescribed. Among patients receiving medication treatment for depression, reception of specialized behavioral health services within the primary care setting was associated with higher likelihood of switching antidepressant medications, and lower likelihood of discontinuing antidepressant treatment. In addition, participation in specialized behavioral health services was associated with higher 6-month medication adherence, but the difference observed in 12-month medication adherence did not achieve statistically significant levels. Future research should evaluate the effects of specialized behavioral health services in the primary care setting on medication-taking behaviors for patients with depression.

OBJECTIVE 4: CLASS OF ANTIDEPRESSANT TREATMENT AND ANTIDEPRESSANT MEDICATION-TAKING BEHAVIORS

The association between class of initial antidepressant treatment and subsequent antidepressant medication-taking behaviors among diabetic patients was evaluated. Based on review of the literature, this study represents the first evaluation of medication-taking behaviors based on initial class of antidepressant prescribed among diabetic patients with depression. None of the *a priori* hypotheses tested under this objective were rejected. After restricting the analytic cohort to only subjects with a diagnosis of diabetes, 109 subjects were included in the analysis. Of these subjects, the majority (n=93) were initiated on SSRI medication treatment.

The number of subjects who exhibited an antidepressant switch were similar in both groups (SSRI: 9.7%, n = 9; non-SSRI 12.5%, n = 2). Antidepressant switch status was not associated with initial class of antidepressant medication at a statistically significant level. In the multivariate model, number of diabetic complications was associated with a 4.40-fold increase in odds of antidepressant switch. The mean number of diabetic complications was higher among patients who switched antidepressant medications compared to those who did not switch (switch: 0.73 ± 0.90; no switch: 0.37 ± 0.58).

It is possible that antidepressant medications may be used in this patient population to directly treat diabetic complications, specifically diabetic peripheral neuropathy. If an individual with neuropathy was initiated on an antidepressant medication that is not effective for treatment of neuropathy, they may be more likely to switch treatment to another antidepressant medication with an indication for this comorbidity. Among the cohort of 109 subjects included in this analysis, a diagnosis indicative of diabetic peripheral neuropathy was observed in 8.3 percent (n=9) of subjects

overall. The frequency of diabetic neuropathy was 27.3 percent (n = 3) among subjects who switched treatment, and 6.1 percent (n = 6) among subjects who did not switch treatment.

Among the 3 subjects with diagnostic coding indicative of neuropathy and who subsequently switched treatment, two were initiated on escitalopram and one on duloxetine. One of the subjects initiated on escitalopram switched treatment to duloxetine, the other to fluoxetine. The subject initiated on duloxetine switched treatment to bupropion. While data suggest variable levels of efficacy for a variety of antidepressant medications in the treatment of neuropathy, duloxetine has an FDA approval for this indication.[223]

The 12-month discontinuation rate was 76.3 percent (n = 71) among subjects initiated on SSRI treatment and 75.0 percent (n = 12) among subjects initiated on SNRI treatment. After covariate control, there was no statistically significant relationship between initial class of antidepressant treatment and antidepressant discontinuation. Among the included covariates, only younger age was associated with antidepressant discontinuation at a statistically significant level.

Initial class of antidepressant treatment was not associated with either 6- or 12-month medication adherence as measured by interval-based MPR. The unadjusted 6-month MPR was 0.56 ± 0.29 for subjects initiated on an SSRI and 0.57 ± 0.32 for subjects initiated on a non-SSRI antidepressant medications. The 12-month MPR was 0.39 ± 0.30 for subjects initiated on an SSRI and 0.42 ± 0.31 for those initiated on a non-SSRI. Among the covariates, only diagnosis other than depression was associated with 12-month MPR; no covariates were associated with 6-month MPR. Diagnosis other than depression was associated with a statistically significant decrease in 12-month MPR.

Among diabetic patients initiated on antidepressant treatment, the lack of a diagnosis of depression present is associated with a 0.15 reduction in antidepressant MPR.

Persistence with antidepressant medication was evaluated as both a continuous measure of time to non-persistence and dichotomous 3- and 12-month persistence measures. There was no statistically significant relationship observed between initial class of antidepressant medication or any of the included covariates and time to anti-depressant non-persistence. Among diabetic patients, the 3-month persistence level was 63.4 percent for subjects initiated on SSRI treatment and 43.8 percent for subjects who were initiated on a non-SSRI treatment. There was no statistically significant relationship observed between class of initial antidepressant medication or any of the included covariates on 3-month persistence status. The 12-month persistence rate was 4.3 percent for subjects started on SSRI treatment and 12.5 percent for subjects started on a non-SSRI medication. After controlling for the included covariates, class of initial antidepressant was not associated with 12-month persistence. Among the covariates, number of diabetic complications was associated with increased likelihood of persistence with antidepressant treatment at 12-months, but not at 3-months.

The statistical power of these analyses may have been insufficient to detect significant differences in the outcomes evaluated. In order to assess the power of these analyses, post-hoc power analysis was conducted using SPSS Sample Power 2.0. For the linear regression of 12-month MPR on antidepressant class at initiation and the included covariates, power was estimated based on an observed increment of 0.189 to R-square for the inclusion of the 9 covariates as a single set in the model, and an increment to R-square of 0.01 for the primary dependent variable of interest (initial class of antidepressant medication). Based on a sample size of 110, this analysis reveals a power

of 0.20 to detect the increment to R-square observed by inclusion of initial class of antidepressant medication prescribed into the model.

Likewise, a post-hoc power analysis was conducted using the observed data from the logistic regression of 3-month antidepressant persistence status on initial class on antidepressant medication treatment. Using a model with only initial class of antidepressant medication included as an independent variable (i.e. inclusion of no covariates in the model), and the observed frequencies of 3-month persistence, a sample size of 110 with a 2-tailed alpha level of 0.05 yields a power of 0.29.

Summary

In summary, the analyses employed for this study failed to reject all of the null hypotheses related to Objective 4. Post-hoc power estimates confirm that the small sample size resulted in insufficient power to reject the null hypothesis based on the observed differences for both the linear regression model evaluating 12-month MPR and the logistic regression model evaluating 3-month persistence. Among the covariates included in the analyses for Objective 4, number of diabetic complications was associated with increased odds of antidepressant switch, and increased odds of 12-month antidepressant persistence. Future research should focus on evaluating the relationship between diabetic complications and antidepressant medication-taking behaviors among patients with a diagnosis of diabetes.

OBJECTIVE 5: ANTIDEPRESSANT ADHERENCE AND GLYCEMIC CONTROL

Hemoglobin A1c values were available for 106 subjects initiated on antidepressant medication. The overall mean hemoglobin A1c for these subjects was 7.41 ± 1.74. Higher level of antidepressant adherence was associated with increased HbA1c values during the follow-up period. The positive association between antidepressant MPR and HbA1c was consistent in analyses of both 6- and 12-month MPR, and after controlling for age, gender, ethnicity, marital status, behavioral health service status, and comorbidity score.

A number of studies have evaluated the effect of antidepressant treatment on glycemic control. Results from these studies suggest that improvements in glycemic control are most closely related to the extent of depressive symptom response. Lustman et al. found that nortriptyline treatment was associated with improvements in depressive symptom severity; however, path analysis revealed a direct hyperglycemic effect attributable to treatment.[157] According to this analysis, while nortriptyline treatment was associated with a hyperglycemic effect, improvement in depressive symptoms with treatment was associated with an indirect beneficial effect on glycemic control. While this study indicates that antidepressant treatment (and specifically nortriptyline treatment) may be associated with hyperglycemia, tricyclic antidepressants were not included in the medication adherence analyses of the current study.

In a placebo-controlled acute phase depression study, fluoxetine treatment was not associated with a statistically significant change in HbA1c level.[160] In this study, depressive symptom remission was likewise not associated with glycemic control. In a long-term maintenance study with sertraline, recovery from depression during acute phase treatment was associated with improved glycemic control; however, during the

maintenance phase of the study, there was no difference observed between sertraline-treated patients and those receiving placebo in terms of glycemic control.[163] Likewise, clinical response to bupropion was associated with improvements in glycemic control during open-label acute phase treatment, but no changes in glycemic control were observed during the maintenance phase of treatment.[158] These prospective studies all incorporated measures of depressive symptom severity, and evaluated the association between improvement in symptoms of depression and glycemic control. The current research did not utilize clinical symptom severity measurements, and was only able to evaluate the relationship between increased levels of antidepressant medication exposure and glycemic control.

A number of recent studies have evaluated antidepressant medication exposure and its association with hyperglycemia, specifically new-onset diabetes. Brown et al. found an increased risk for new-onset diabetes for patients taking SSRI/TCA combination therapy compared to TCA monotherapy.[170] In this study, SSRI monotherapy was associated with lower risk of observing new-onset diabetes compared to TCA monotherapy. Rubin et al. found that antidepressant medication exposure was a risk factor for developing new-onset diabetes among a group of subjects with high risk for developing diabetes.[171] Intermittent antidepressant exposure was not associated with a statistically significant increase in odds of diabetes diagnosis, while continuous antidepressant use was associated with a significant increase in risk. Research conducted by Andersohn et al. likewise suggests that the extent of antidepressant exposure is a key factor in risk of diabetes associated with antidepressant exposure.[172]

The findings of the current study suggest that increased level of antidepressant exposure may be associated with impaired glycemic control. A number of factors may explain the association between antidepressant medication exposure and hyperglycemia

among diabetic patients. First, higher levels of antidepressant exposure may be a marker for increased severity of depressive symptomatology. The association between depressive symptomatology and hyperglycemia in diabetic patients has been established in a number of studies.[55] The relationship between depressive symptoms and hyperglycemia has been attributed to physiological factors, psychosocial factors, and self-care behaviors.[126]

Second, antidepressant medication use may be associated with metabolic side effects that alter glycemic control in diabetic patients. Raeder et al. found that SSRI use was associated with obesity and hypercholesterolemia, and that this effect varied based on the specific medication evaluated.[174] It is not unexpected that there would be variability in the relationship between antidepressant use and metabolic side effects based on the specific pharmacological properties of the various agents. Paroxetine and mirtazapine, for example, have been associated with weight gain in patients treated for depression.[31,224] The current study did not evaluate the relationship between antidepressant exposure and hyperglycemia based on the individual agent used. SSRI medications accounted for the vast majority (83.0%) of antidepressant treatment in this analysis. Sertraline was the most frequently prescribed individual antidepressant medication overall (50.0%).

A significant limitation in this analysis was the lack of control for pre-index HbA1c levels. Inclusion of these data would have limited the sample size for this analysis to 24 subjects. In addition, this analysis was unable to incorporate HbA1c measures from a precisely defined time point during the follow-up period. Hemoglobin A1c data were collected during the course of usual care within the clinics, and were incorporated as available into this analysis. The period of time post-index during which HbA1c values were available was broad. The mean number of days between initial prescription claim for an antidepressant medication and observation of HbA1c value was 428 (± 169) days

with a range of 122 to 1,100. This broad timeframe, although necessary to achieve a sufficient sample size, represents a significant threat to the internal validity of this analysis.

Summary

Higher level of antidepressant medication adherence was associated with increased HbA1c levels. A number of factors may explain the observed relationship. Increased levels of antidepressant medication exposure may represent a marker for depressive disease state severity. In addition, specific antidepressant medication may be associated with effects on metabolic factors that affect glycemic control. The current analysis is limited in that HbA1c values were observed over a broad period of time post initiation of antidepressant treatment.

LIMITATIONS

Clinic service eligibility

Data for subjects included in this study were obtained from the existing administrative and clinic records for patients receiving care within the clinic network. In order for a subject to be included in the various components of this study, the individual was required to display a period of continuous service eligibility. This requirement was necessitated by the nature of the study design, which followed subjects from an index event occurring in the past, and evaluating clinical outcomes over a predetermined period of time after that event.

An indigent clinic network served as the source of data for this research. Service eligibility is based on income level and the Federal Poverty Index guidelines. When an individual is determined to be eligible for clinic services, he/she are assigned a period of service eligibility that may last for between 3 and 12 months. After the end of the initial period of eligibility, the individual must undergo a new determination of eligibility in order to continue receiving care within the clinic. The period of time between the lapse in service coverage and the renewal of coverage is variable and is associated with clinical follow-up. That is, once an individual's initial period of service eligibility expires, his/her service eligibility is not automatically reviewed at the conclusion of the period, but rather is only re-evaluated once the individual presents for services after the expiration of their service coverage. For these reasons, there are a number of situations that may result in a temporary lapse of service coverage, including failure to meet eligibility requirements and failure to present to the clinic for services once eligibility has terminated. In order to construct a study cohort of subjects with continuous clinic eligibility, a gap of 90 days between discrete eligibility periods was allowed.

The continuous service eligibility requirement resulted in a significant reduction in the number of subjects with data available for analysis. Initially, 34,512 subjects were identified who had clinic data available for extraction; however, after applying the continuous service eligibility criteria, the number of subjects available for inclusion in the analytic cohort for Objective 1 was 2,886. Likewise, the number of subjects included in the analytic cohort for Objectives 3 through 5, which required 18 months of continuous service eligibility and an index antidepressant prescription claim, was only 455. Applying diagnostic confirmation of the presence of depression further reduced the number of subjects with an index antidepressant claim to 277. Further reductions in sample size were observed for the analyses related to Objective 5, which required HbA1c data during the follow-up period after an index antidepressant prescription claim.

It is not completely clear in what way individuals with long periods of continuous eligibility differ systematically from individuals with short periods of continuous eligibility, and how the selection of individuals with longer periods of continuous service eligibility may have biased the study cohorts. It is possible that a longer permissible "service gap" between service periods would have resulted in a less significant reduction in the sample size available for study inclusion. The 90 day "gap period" was determined with the input and feedback of clinic administrators and information technology personnel familiar with the operational environment of the clinic. While a longer gap period would have increased the available sample size, it would have also allowed for subjects receiving care in other indigent clinic networks for a substantial portion of the observation period to be included in the analyses.

Use of Secondary Databases for Clinical Research

The use of administrative and healthcare claims data as a resource for medical outcomes research in non-experimental studies is common; however, there are a number of considerations and limitations to the use of these data.[225,226] Data for the current study were collected from a range of health information systems, including administrative, clinical, and pharmacy records. Administrative data, including eligibility determinations and clinic encounters, were utilized. In addition, clinical data such as diagnoses and laboratory test results were incorporated into this research. In terms of pharmacy data, prescription claims from community and onsite pharmacies were utilized.

As opposed to research utilizing only prescription claims, a strength of this study was the ability to incorporate patient-level diagnostic and clinical data. Although the inclusion of these data allowed for analysis of the relationship between medication utilization and clinical status (e.g., HbA1c values), these analyses were limited due to lack of availability of HbA1c data for the vast majority of subjects. In addition, very few subjects with HbA1c data in the post-index period had pre-index values that could be incorporated in the model, as discussed previously. Therefore, inclusion of clinical data as an outcome measure was a "double-edged sword," contributing its own unique limitations.

Data Validity

A significant limitation to the use of secondary data is the threat to validity posed by missing, incomplete, or inaccurate data within the information technology systems. Data for some subjects may be missing or incomplete due to inherent limitations of the database system (e.g., a limit on the number of diagnoses recorded for each clinic encounter), patient-specific factors related to healthcare consumption (e.g., using an "out-

of-network" provider), or error or oversight on the part of clinic staff (e.g. erroneous coding or data input). In addition, variables which may affect study outcomes (e.g., income level, smoking status, body weight, family history) may not be available in administrative or clinical database systems in an extractable form.

Diagnostic Data

While the ability to incorporate diagnostic data into this research offers some advantages, the use of administrative claims data to establish medical diagnosis is not without limitation. First, due to limitations inherent in the design of the systems utilized for this study, a maximum of four diagnostic codes can be associated with a given clinic encounter. Therefore, some diagnoses may not be captured during a given encounter when, in fact, the diagnosis was present. Diagnoses captured in the system may also change over time; for example, a diagnosis may be recorded in one encounter but not another occurring at a later time point. In addition, diagnoses present in administrative records may be representative of a variety of factors influencing healthcare provider behavior, rather than purely clinical considerations.[227]

The validity of database diagnostic codes is site-, provider-, and disease state-specific.[225] Research suggests that diagnostic codes may have variable validity for different psychiatric conditions. Rawson et al. found a high level of agreement between administrative data and individual medical charts for patients with schizophrenia, but lower concordance for patients for depression.[228] Rawson speculates that their finding may be related to the severity and/or specificity of certain psychiatric diagnoses compared to others. Medical disorders, and especially psychiatric disorders, that are more severe and more precisely defined may be more likely to be accurately captured in

diagnostic codes present in administrative data. There has been no systematic evaluation of diagnostic data reliability and validity reported for the CommUnity care clinic setting.

Prescription Claims

In addition to the factors mentioned previously affecting all secondary healthcare databases, there are a number of factors unique to the evaluation of medication adherence based on prescription claims data. The validity of adherence and persistence measures based on prescription claims data are predicated on a number of assumptions. First, it is a fundamental assumption that the patient actually takes the medication that he/she receives from the pharmacy. Prescription claims are only an indication that the individual received the prescription medication from the pharmacy, not necessarily that the individual ingested the medication. In this manner, prescription claims data are only a surrogate for medication-taking. While the use of medication claims data to measure adherence and persistence is based on these fundamental assumptions, measures based on claims data may be less susceptible to recall bias or inaccuracy than self-report measures.[227] Second, evaluation of medication adherence based on claims data assumes comprehensiveness of the prescription data. That is, that all prescription medication fills are captured in the claims database. Medication provision for individuals who receive medications from other sources (e.g., samples) is not captured in the prescription claims database. In the current study setting, patients with prescription claims were receiving medical assistance to assist them in paying for their prescription medication. This does not, however, completely remove the possibility that patients with prescription assistance were utilizing medications procured through sources outside the scope of study data collection.

Generalizability

The population from which the study cohorts were constructed was an indigent primary care population. Results from the current research may not be applicable to patients treated in other clinical settings. Patients who were included in the current study were classified, by nature of their eligibility for services, as being at or below 200% of the Federal Poverty Index Guidelines. Patients from lower socioeconomic levels have higher rates of many medical conditions, including chronic medical conditions such as diabetes.[229-232] The relationship between socioeconomic status and health is complex, but may be related to education, environmental factors, health beliefs, access to healthcare resources or a variety of other factors.[233-236]

In addition, the patient population evaluated in this study was classified predominantly as White Hispanic and female gender. These factors may limit the generalizability of the study results to populations of patients representing differing demographic makeup. In addition, all subjects in this study were receiving care in a regional community clinic network located in Central Texas, which may limit the generalizability to other geographical regions.

FUTURE RESEARCH

This study represents an evaluation of the relationships between diabetes and depression and antidepressant medication utilization patterns among indigent patients receiving community healthcare services. This area, specifically research in underserved populations, is an area of medical outcomes research with room for substantial growth. Factors associated with medical outcomes in the non-indigent patient population may not be generalizable to the indigent care population and their unique needs. Continued research in this specific population is necessary in order to help clinicians and researchers understand these needs, and in order to design and implement tailored interventions for these traditionally underserved patient populations.

In terms of the specific area addressed by this study, future research is needed to explore the epidemiological relationship between diabetes and depression in this patient population. Future research in this area should specifically evaluate the association between race/ethnicity and epidemiological and clinical outcomes associated with diabetes and depression. While research has been conducted evaluating cultural and racial factors associated with a variety of psychiatric disorders and their treatment, very little research has been conducted specifically in these areas with patients displaying co-occurring diabetes and depression. In light of the increased risk for both diabetes and depression among minority groups such as Hispanics, research that increases the understanding and ability of medical providers to communicate healthcare information in a culturally competent manner is essential. Research establishing the unique phenomenology of depression among minority patient populations with depression may assist in understanding the results of the current research, as well as previous research suggesting culture-specific epidemiology of depression among diabetic patients.

The role and outcomes associated with integrated behavioral health services in the primary care setting should be addressed by future research. The current study found that behavioral health interventions were associated with outcomes related to medication-taking behaviors. Studies that focus on this specific relationship, and other clinical outcomes associated with integrated behavioral health interventions, are necessary.

The association between antidepressant medication exposure and glycemic control in diabetic patients deserves further research. Research suggests that antidepressant exposure may increase risk for development of new-onset diabetes, and the current research suggests that a relationship may exist between antidepressant exposure and hyperglycemia in diabetic patients. An ideal research design would allow for the incorporation of measures of depressive symptom severity and both pre- and post-index measures of glycemic control. The current study was limited in that post-index glycemic control was evaluated over an extended period of time, and pre-index HbA1c values were not available for a sufficient number of patients. In addition, the current study did not control for depressive symptom severity. A comprehensive clinical data resource will be required to rigorously evaluate this relationship. Alternatively, in light of the limitations of secondary database systems, prospectively collected data would appear to be the best method available to address this research topic.

A pressing issue as relates to the current research is the need for characterizing the data sources utilized for this study. Specifically, there is a need to evaluate the data integrity, reliability, and validity of the administrative and clinical database sources within the clinic network. In addition, analyses evaluating the relationship between demographic and clinical factors associated with continuous clinic service eligibility are needed.

One significant limitation of the current study was the requirement for continuous clinic services eligibility within a single community healthcare "network." As advances in health information technology and medical data sharing among indigent healthcare networks evolves, future research should account for the transient and intermittent nature of medical care that exists in this patient population. Studies need to be designed to take into account the difficulty in constructing substantial cohorts of patients with longitudinal data. In the future, programs that attempt to facilitate communication between disparate clinic networks may allow for broader determinations of continuous care across multiple clinic networks, and may allow for tracking individuals as they transition in and out of inter-network clinic care.

To the extent that outcomes evaluations are necessary to provide "real-world" assessment of clinical outcomes and clinic quality improvement feedback, a sufficient health information infrastructure is necessary that meets the administrative needs of the clinic setting, as well as the requirements necessary to facilitate rigorous outcomes research. While the use of clinical information obtained from administrative databases is common in outcomes research, there is often a balance between study considerations and issues related to data validity and reliability. The current research study was limited by the lack of clinical data available for outcomes research. As our health information technology evolves, researchers should be involved in the design of these systems to the extent that their input will inform creation of information systems that not only serve the interests of administrative and clinical staff, but can be utilized to produce clinically meaningful and valid outcomes evaluations.

In addition to establishing improvements in the area of health information technology and enhanced researcher interface to these systems, future research in this area should integrate prospective outcomes evaluations within community clinics.

Prospective evaluations will allow researchers to address and account for many of the limitations inherent to retrospective evaluations such as the current study.

CONCLUSION

This study evaluated the associations between diabetes, depression, and antidepressant medication-taking behaviors among indigent care patients. Diabetes was found to be associated with decreased odds of observing an incident diagnosis of depression. Greater age, female gender, and White non-Hispanic ethnicity were independent risk factors for a diagnosis of depression among clinic patients evaluated. No statistically significant relationships were observed for any of the demographic or clinical factors and incident depression among diabetic patients in the *a priori* risk factor analyses. Exploratory analyses revealed that demographic factors including gender and ethnicity may be associated with increased risk of diabetic patients developing depression.

Despite a significant amount of research linking diabetes with increased risk for depression, the current study found that a diagnosis of diabetes was associated with decreased probability of observing a clinical diagnosis of depression among patients receiving care in an indigent primacy care setting. In terms of the relevance of these findings to clinical practice, these findings suggest that under-recognition and under-diagnosis of depression in the indigent care setting may be a significant problem. Systematic screening for common psychiatric conditions such as depression is important in the primary care setting, and may be especially important among patients with chronic medical conditions such as diabetes.

Diabetes was associated with higher rates of initial SSRI prescribing for the treatment of depression, but was not associated with either switch or discontinuation of antidepressant treatment. Differences observed in antidepressant medication adherence and adherence in the current study may have been driven by differences in prescribing

patterns among diabetic patients compared to non-diabetic patients, specifically in terms of a greater days supply of medication associated with the initial antidepressant prescription claim for diabetic patients. Class of initial antidepressant medication did not appear to be associated with any of the medication-taking outcomes evaluated, although this may have been related to small sample size and insufficient study power.

This study found an association between higher levels of antidepressant adherence and worsened glycemic control in diabetic patients. These findings suggest that an increased level of antidepressant exposure is not only associated with new-onset diabetes, but may also be associated with impaired glycemic control among patients who already have diabetes. These findings, however, are limited due to the period of time during which HbA1c data were observed and the lack of control for baseline HbA1c level, and will need to be replicated in future studies.

Results of the current study suggest that a prevalent diagnosis of diabetes is associated with a reduced risk for a diagnosis of new-onset depression in indigent care patients. Further research is necessary to evaluate the effect that chronic comorbid medical conditions such as diabetes may have on antidepressant medication-taking behaviors, and relationship between antidepressant exposure and glycemic control.

Appendices

APPENDIX A. RETROSPECTIVE STUDIES OF MEDICATION ADHERENCE IN DIABETES BASED ON PHARMACY CLAIMS DATA

Author, year	n	Medications	Drug Utilization Measure(s)	Adherence	Categorical Adherence	Persistence
Venturini, 1999	786	SU	No. of days out of medication/sum of days in all intervals Morisky survey	83%	High: 43.9% Medium: 41.9% Low: 14.2%	N/A
Boccuzzi, 2001	85,888	SU, MET, TZD, AGI, MEG	Adherence: sum of days supply/duration of therapy persistence: continuous access to ≥ 1 days' supply of medication	12 month adherence: MET: 76.4% SU: 80.1 % TZD: 83.0% AGI: 70.4% MET: 69.8%	N/A	12 month persistence: MET: 60.3% SU: 56.2% TZD: 43.2% AGI: 31.1% MET: 48.1%
Catalan, 2001	Young: 216 Seniors: 366	Acarbose	Ever-renew: frequency of renewal of index prescription at any point during follow-up period Compliant-renew: frequency of renewal of index prescription with a gap equivalent to 1/2 the days supply Persistence: Number of days between first fill and first failure to refill prescription	Ever-renew: 73%, 80% Compliant-renew: 60%, 65%	N/A	79 days, 101 days
Dailey, 2002	23400	ODM and/or insulin	Adherence: sums of days' supply/number of days in follow-up period Persistence: Number of days with continuous medication therapy, with a grace period between fills equal to 0.5 times the days supply of the preceding fill	1 year follow-up: SU: 64.64% MET: 65.06% SU + MET: 44.42% 2 year follow-up SU: 60.54% MET: 63.07% SU + MET: 35.76%	N/A	1 year follow-up: SU: 183.1 days MET: 183.8 days SU + MET: 111.1 days 2 year follow-up SU: 274.3 days MET: 296.7 days SU + MET: 121.9 days
Dezii, 2002	992	Glipizide	Adherence: sum of the days supply/days in observation period Persistence: number of days with continous medical	QD: 60.5% BID: 52.0%	N/A	12 month persitence: QD: 44.4% BID: 35.8%

n, number of subjects; N/A, not applicable or not reported; SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; MEG, meglidinide ; ODM, any oral diabetic medication

APPENDIX A. RETROSPECTIVE STUDIES OF MEDICATION ADHERENCE IN DIABETES BASED ON PHARMACY CLAIMS DATA (CONTINUED)

Author, year	n	Medications	Drug Utilization Measure(s)	Adherence	Categorical Adherence	Persistence
Donnan, 2002	2849	SU or MET	Sum of the days' supply/days in observation period	N/A	SU: 31% MET: 34%	N/A
Evans, 2002	2537	SU or MET	Sum of days' supply/days in study period	SU: 93.7% MET: 85.4%	SU: 63% MET: 50%	N/A
Mellkian, 2002	1815	SU+MET	Days supply of medication/days in study period, days supply of medication/nubmer of days between first and last fill	Combination tablet: 77.0% two-tablet treatment: 54.0%	N/A	N/A
Morningstar, 2002	3358	SU or MET	CMA: sum of day's supply between the first and last fill/sum of days' between first and last fill CMG: accumulated gap days/total number of days between the first and last fill CMOS: accumulated oversupply days/total nubmer of days between first and last fill	CMA: 86% CMG: 16% CMOS: 3%	N/A	N/A
Schectman, 2002	810	SU, MET, AGI, TZD	Days supply/days in treament interval	Overall MPR: 79.7% Whites: 82.0% Blacks: 76.5% (p=0.0002 vs. whites)	N/A	N/A
Spoelstra, 2002	411	SU, MET,	Total number of days with medication/number of days of observation	85.3%	N/A	N/A
Balkrishnan, 2003	775	ODM, insulin,	Sum of days supply/days in treatment period	71-78% each year over 5 year period	N/A	N/A
Kogut, 2004	1067	SU, MET	Sum of the days' supply/number of days between first and last fill	N/A	SU: 87.9% MET: 81.9%	N/A

n, number of subjects; N/A, not applicable or not reported; SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; MEG, meglidinide ; ODM, any oral diabetic medication

APPENDIX A. RETROSPECTIVE STUDIES OF MEDICATION ADHERENCE IN DIABETES BASED ON PHARMACY CLAIMS DATA (CONTINUED)

Author, year	n	Medications	Drug Utilization Measure(s)	Adherence	Categorical Adherence	Persistence
Lau, 2004	900	SU, MET, TZD,	Sum of days supply/number of days between 1st and last fill	N/A	71.2%	N/A
Pladevall, 2004	677	MET	Number of days with gaps in medication refill/number of days in observation period	MET: 57%	N/A	N/A
Hertz, 2005	6090	SU, MET, MEG,	Adherence: sum of days supply/observation period Early non-persistence: failure to fill a second prescription Persistence: length of time between first fill and and the	N/A	53.8%	Early non-persistence: 10.5% 12 month non-persistence: 37.0%
Lawrence, 2006	2741	SU, MET	Sum of days supply/days in evaluation period	SU: 76% MET: 69%	N/A	N/A
Ho, 2007	11532	SU, MET, TZD	Sum of days supply/observation period	N/A	79.7%	N/A
Adams, 2008	1806	ODM	Milligrams dispensed/amount prescribed per month	At 6 months Whites: 78.3% Blacks: 72.7% At 12 months: Whites: 77.6% Blacks: 71.7%	N/A	N/A
Rozenfeld, 2008	2741	SU, MET, AGI,	Sum of days supply/duration of therapy	Overall MPR: 81.3% SU: 81.8% MET: 80.7% TZD: 82.0%	Overall: 65.4% SU: 65.8% MET: 63.9% TZD: 69.4%	N/A

n, number of subjects; N/A, not applicable or not reported; SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; MEG, meglidinide ; ODM, any oral diabetic medication

APPENDIX B. STUDIES EVALUATING THE RELATIONSHIP BETWEEN DIABETIC MEDICATION ADHERENCE AND GLYCEMIC CONTROL

Author, year	n	Design	Diabetic Medications	Data Source	Adherence Measure	Findings	Covariates
Schectman, 2002	810	Retrospective cohort	SU MET TZD AGI	Pharmacy claims, clinic data	MPR	10% increase in MPR associated with 0.16% lower HbA1c ($p< 0.0001$) and a 0.13% greater decrease in HbA1c ($p < 0.0001$) over 15 month study period.	Age Gender Ethnicity Income/copay No. oral agents Insulin use No. HbA1c levels No. encounters Continuity index
Guilliausseau, 2003	11896	Prospective cohort	SU MET AGI	NR	Patient self-report	HbA1c significantly lower among subjects reporting no missed doses of medication compared to those reporting missing more than one dose per week (7.1 vs. 8.5%, $p<0.01$).	None
Krapek, 2004	301	Prospective cohort	SU MET AGI TZD	Survey, clinic data	Morisky survey	Good adherence (Morisky score ≥ 3) associated with a 10% decrease in total HbA1c ($p<0.001$)	Age Gender Ethnicity No. diabetic medications Presence of DM complications Duration of DM BMI Education level Practice site Type of insurance

n, number of subjects; NR, not reported; SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; MEG, meglitinide ; DM, diabetes mellitus; MPR, medication possession ratio; SBP, systolic blood pressure; BMI, body mass index; ODM, oral diabetic medication regimen

APPENDIX B. STUDIES EVALUATING THE RELATIONSHIP BETWEEN DIABETIC MEDICATION ADHERENCE AND GLYCEMIC CONTROL (CONTINUED)

Author, year	n	Design	Diabetic Medications	Data Source	Adherence Measure	Findings	Covariates
Pladevall, 2004	677	Retrospective cohort	MET	Pharmacy claims, clinic data	CMG	10% increase in nonadherence associated with a 0.14% increase in HbA1c (p<0.01)	Age Gender Ethnicity BMI No. total medications No. outcome measures
Lawrence, 2006	2995	Retrospective cohort	SU MET	Pharmacy claims	MPR	Negative correlation between HgA1c and MPR for both SU (r=-0.295, p<0.001) and MET (-0.285, p<0.001).	None
Adams, 2008	1806	Retrospective cohort	NS	Clinic data	MPR	10% increase in MPR associated with decrease in HbA1c (blacks, -0.02%; whites 0.03%; p-values not reported)	Race Age Gender Comorbidity SBP Cholesterol level BMI Baseline HbA1c Baseline medications No. of physician visits Test strip use Therapy intensification Medication adherence
Rozenfeld, 2008	2741	Retrospective cohort	SU MET TZD AGI MEG	Pharmacy claims	MPR	10% increase in adherence associated with a 0.1% decrease in HbA1c (p = 0.0004)	Age Gender Baseline HbA1c Chronic disease score Medication burden Provider demographics ODM regimen

n, number of subjects; NR, not reported; SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; MEG, meglitinide ; DM, diabetes mellitus; MPR, medication possession ratio; SBP, systolic blood pressure; BMI, body mass index; ODM, oral diabetic medication

APPENDIX C. STUDY DATA MATRIX: DATA SOURCES AND DATA ELEMENTS

Dataset	NHIS	Eligibility file	Pharmacy		Labs
			Community	Class A	
Demographic data					
Study ID					
Age		x			
Gender	x				
Ethnicity	x				
Marital status	x				
Primary care provider	x				
Dates of eligibility		x			
Visit/Encounter data					
Encounter type	x				
Location	x				
Physician	x				
Date of service	x				
Diagnosis codes	x				
Procedure codes	x				
Lab data					
Test	x				x
Lab date	x				x
Lab result	x				x
Ordering provider	x				x
Prescription data					
RX fill date			x	x	
Dispense date			x	x	
Original date			x	x	
Prescriber			x	x	
NDC			x	x	
Drug label			x	x	
Quantity			x	x	
Days supply			x	x	
Refills allowed			x	x	
Fill number			x	x	

NHIS, NextGen Health Information System; NDC, National Drug Code.

APPENDIX D. STUDY VARIABLES, VARIABLE CODING, VARIABLE TYPE, AND SOURCE

Variable	Value(s)	Type	Source
Variables of interest			
Diagnosis of depression	0 = diagnosis not present; 1 = diagnosis present	Dichotomous	NHIS
Diagnosis of diabetes	0 = diagnosis not present; 1 = diagnosis present	Dichotomous	NHIS
Antidepressant MPR	range = 0-1	Continuous	EPR
Time to AD non-persistence	Continuous (days)	Continuous	EPR
Antidepressant class	0 = SSRI; 1 = non-SSRI	Dichotomous	EPR
Antidepressant switch	0 = no switch; 1 = switch	Dichotomous	EPR
Antidepressant discontinuation	0 = no discontinuation; 1 = discontinuation	Dichotomous	EPR
Glycemic control	Continuous (Hemoglobin A1c %)	Continuous	Laboratory
Covariates			
Age	Continuous, possible range 18-64	Continuous	NHIS
Gender	0 = female; 1 = male	Dichotomous	NHIS
Ethnicity	0 = White Hispanic; 1 = non-White Hispanic; 2 = African-American; 3 = Other or Unknown	Categorical	NHIS
Marriage status	0 = Single; 1 = Married; 2 = Other or Unknown	Categorical	NHIS
Behavioral health service status	0 = not receiving services; 1 = receiving services	Dichotomous	NHIS
Diabetic complications	Continuous (number of complications)	Continuous	NHIS
Charlson score	Continuous, possible range 0-7	Continuous	NHIS
Ethnicity†	0 = White Hispanic; 1 = other race/ethnicity	Dichotomous	NHIS
Diagnosis of depression†	0 = diagnosis present; 1 = diagnosis not present	Dichotomous	NHIS

NHIS, NextGen health information system; EPR, electronic pharmacy records; AD, antidepressant; MPR, medication possession ratio; SSRI, selective serotonin reuptake inhibitor.

† incorporated as a covariate for Objective 4 analyses only

APPENDIX E. DIAGNOSES, WEIGHTS, AND ICD-9 CM DIAGNOSTIC CODES FOR DIAGNOSES USED TO CALCULATE CHARLSON SCORE

Diagnosis	Charlson weight	ICD-9 code(s)
Myocardial infarction	1	410.xx, 412.xx
Congestive heart failure	1	402.01, 402.11, 402.91, 425.xx, 428.xx, 429.3x, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Peripheral vascular disease	1	440.xx, 441.xx, 442.xx, 443.xx, 447.1x, 785.4x
Cerebrovascular disease	1	362.34, 430.xx-436.xx, 437.0x-437.1x, 437.9x, 438.xx, 781.4x, 784.3x, 997.0x
Dementia	1	290.xx, 331.0x-331.2x
Chronic pulmonary disease	1	415.0x, 416.8x-416.9x, 491.xx-494.xx, 496.xx
Rheumatological disease	1	710.xx, 714.xx
Peptic ulcer disease	1	531.xx - 534.xx
Mild liver disease	1	571.2x, 571.5x-571.6x, 571.8x-571.9x
Diabetes	1	250.0x-250.3x
Diabetes with complications	2	250.4x-250.9x
Paralysis	2	342.xx, 344.xx
Renal disease	2	585.xx-586.xx
Any malignancy, including leukemia and lymphoma	2	140.xx-171.xx, 174.xx-195.xx, 200.xx-208.xx, 273.0x, 273.3x
Moderate to severe liver disease	3	572.2x-572.4x, 456.0x-456.2x
Metastatic solid tumor	6	196.xx-199.xx
Acquired immune deficiency syndrome	6	042.xx-044.xx

APPENDIX F. DIABETIC COMPLICATIONS AND ASSOCIATED ICD-9 CM DIAGNOSTIC CODES

Diagnosis	ICD-9 code(s)
Retinopathy	
Diabetic ophthalmologic disease	250.5x
Background retinopathy	362.01
Other retinopathy	362.1x
Retinal edema	362.83
Cystiod macular degeneration	362.53
Other retinal disorders	362.81, 362.82
Proliferative retinopathy	362.02
Retinal detachment	361.xx
Blindness	369.xx
Vitreous hemorrhage	379.23
Nephropathy	
Diabetic nephropathy	250.4x
Acute glomerulonephritis	580.xx
Nephrotic syndrome	581.xx
Hypertension, nephrosis	581.81
Chronic glomerulonephritis	582.xx
Nephritis/nephropathy	583.xx
Chronic renal failure	585.xx
Renal failure NOS	586.xx
Renal insufficiency	593.9x
Neuropathy	
Diabetic neuropathy	250.6x, 356.9x
Amyotrophy	358.1x
Cranial nerve palsy	951.0x, 951.1x, 951.3x
Mononeuropathy	354.xx, 355.xx
Charcot's arthropathy	713.5x
Polyneuropathy	357.2x
Neurogenic bladder	596.54
Autonomic neuropathy	337.0x, 337.1x
Gastroparesis/diarrhea	545.5x, 536.3x
Orthostatic hypotension	458.0x

APPENDIX F. DIABETIC COMPLICATIONS AND ASSOCIATED ICD-9 CM DIAGNOSTIC CODES (CONTINUED)

Diagnosis	ICD-9 code(s)
Cerebrovascular	
Transient cerebral ischemia	435.xx
Stroke	431.xx, 433.xx, 434.xx, 436.xx
Cardiovascular	
Atherosclerosis	440.xx
Other ischemic heart disease	411.xx
Angina pectoris	413.xx
Other chronic ischemic heart disease	414.xx
Myocardial infarction	410.xx
Ventricular fibrillation, arrest	427.1x, 427.3x
Atrial fibrillation, arrest	427.4x, 427.5x
Other arteriosclerotic cardiovascular disease	429.2x
Old myocardial infarction	412.xx
Heart failure	428.xx
Atherosclerosis, severe	440.23, 440.24
Aortic aneurysm/dissection	441.xx
Peripheral vascular disease	
Diabetic peripheral vascular disease	250.7x
Other aneurysm	442.3x
Peripheral vascular disease	443.81, 443.9x
Foot wound + complication	892.1x
Claudication, intermittent	443.9x
Embolism/thrombosis	444.22
Gangrene	785.4x
Gas gangrene	000.4x
Ulcer of lower limbs	707.1x

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Vita

Brandon Thomas Suehs was born in Austin, TX on February 24, 1978 to Patricia Katherine Suehs and Thomas Michael Suehs. He received his Doctor of Pharmacy degree from the University of Texas at Austin, College of Pharmacy in 2004. He was registered as a licensed pharmacist in August, 2004 by the Texas State Board of Pharmacy. Upon graduation, Dr. Suehs undertook a specialty residency in psychiatric pharmacy practice. This residency provided Dr. Suehs with the opportunity to work in a variety of mental health practice sites, including the Austin State Hospital, Seton Shoal Creek Hospital, and Bluebonnet Trails Community Mental Health & Mental Retardation Center. Concurrent to beginning his pharmacy residency experience, Dr. Suehs enrolled in the graduate program of the College of Pharmacy Division of Pharmacy Administration at the University of Texas at Austin. Dr. Suehs has lectured in courses including Introduction to Therapeutics and Psychiatric Pharmacy Practice and Drug Treatment of Mental Disorders. In addition, Dr. Suehs has taught on a variety of pharmacology and therapeutics topics for the Austin Medical Education Programs. Dr. Suehs is married to Jennifer Angelo Suehs, MA and currently resides in Austin, TX. In 2009, Jennifer and Brandon celebrated the birth of their daughter, Evangeline Diana Suehs.

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